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U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

Examiner # (Mandatory): 73633 Requester's Full Name: DAVE TRONG NGUYEN

Art Unit 1633 Location (Bldg/Room#): CM1 12B15 Phone (circle 305 306 308) 2024

Serial Number: 08/727,519 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention: Novel polymeric complexes for DNA transfection

Inventors (please provide full names): Patrick Midoux, Michel Monsigny

Earliest Priority Date: 11/15/1996

Keywords (include any known synonyms registry numbers, explanation of initialisms):

polymer conjugate
dna, nucleic, polynucleotide, vector, plasmid
polymer formed from monomers having free NH_3^+ groups 10% of which can be substituted by residues which can be protonated in a weakly acidic medium, thereby causing destabilization of cell membranes

proviso: all the free NH_3^+ make up at least 30% of the # of monomers of the skeleton of the polymeric conjugate

Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

Please search for a polymer conjugate or polymer having free NH_3^+ groups substituted by residues in claims 26, 27, and 37

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 12C14 Tel: 305-4053

Please search claim 29 wherein R is a residue with an Imidazole nucleus or the formula of claim 30,

Please search claim 32.

The claim sheets are attached.

STAFF USE ONLY

Searcher: Hanley
Searcher Phone #:
Searcher Location:
Date Picked Up:
Date Completed: 10/31
Clerical Prep Time: S:90/T:60
Terminal Time: STR:140/T:722
Number of Databases:

Type of Search

___ N.A. Sequence
___ A.A. Sequence
3 Structure (#)
___ Bibliographic
___ Litigation1
___ Fulltext
___ Procurement
___ Other

Vendors (include cost where applicable)

___ STN
___ Questel/Orbit
___ Lexis/Nexis
___ WWW/Internet
___ In-house sequence systems (list)
___ Dialog
___ Dr. Link
___ Westlaw
___ Other (specify)

=> d bib abs hitstr l47 1

L47 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:608589 HCAPLUS
DN 133:198688
TI Multiparticulate formulations containing polycationic **complexes**
IN Hardee, Gregory E.; Tillman, Lloyd G.; Mehta, Rahul C.; Teng, Ching-Leou
PA Isis Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000050050	A1	20000831	WO 2000-US4662	20000223

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-256515 19990223

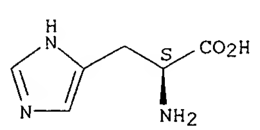
AB The present invention is related to non-parenteral multiparticulate formulations capable of transporting therapeutic, prophylactic and diagnostic agents across mucosal membranes such as gastrointestinal, buccal, nasal, rectal and vaginal. Formulations comprise a plurality of carrier particles, an agent to be delivered across a mucosal membrane, and a penetration enhancer. The drug is adhered to the surface of the carrier particle or is impregnated within by electrostatic, covalent or mech. forces. PLGA was dissolved in hexafluoroacetone2 and **oligonucleotide** ISIS-2302 was dissolved in water. The aq. and polymer solns. were combined to give a dispersed phase. A continuous phase was prepd. by dissolving sorbitan sesquioleate in cottonseed oil. The dispersed phase was then slowly added to the continuous phase, while mixing and continued mixing for about 3 h and increasing the temp. to 50.degree. to evap. the volatile solvent.

IT **26062-48-6**, Poly(Histidine) **26854-81-9**, Poly(Histidine)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiparticulate formulations contg. polycationic **complexes**)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

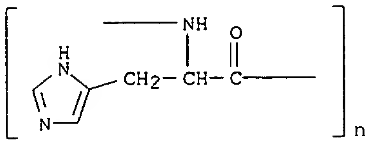
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RE.CNT 3
RE

(1) Gao; US 5795587 A 1998
(2) Hedley; US 5783567 A 1998 HCAPLUS
(3) Isis Pharmaceuticals Inc; WO 9849348 A1 1998 HCAPLUS

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=> d bib abs hitstr l47 2

L47  ANSWER 2 OF 23  HCAPLUS  COPYRIGHT 2000 ACS
AN   2000:314492  HCAPLUS
DN   132:346610
TI   Enhanced vaccines
IN   Hellman, Lars T.
PA   Resistentia Pharmaceuticals AB, Swed.
SO   PCT Int. Appl., 50 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   WO 2000025722     A2   20000511      WO 1999-SE1896   19991021
     WO 2000025722     A3   20001012
         W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
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             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1998-106652    19981102
     US 1999-401636    19990922
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AB The invention relates to methods and materials involved in the treatment and prevention of various diseases such as infections and IgE-related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of IgE antibodies within a mammal by reducing the amt. of total and receptor bound IgE antibodies in the mammal. In addn., the invention provides vaccine **conjugates**, immunogenic polypeptides, **nucleic acid** mols. that encode immunogenic polypeptides, host cells contg. the **nucleic acid** mols. that encode immunogenic polypeptides, and methods for making vaccine **conjugates** and immunogenic polypeptides as well as **nucleic acid** mols. that encode immunogenic polypeptides. Further, the invention provides an IgE vaccine that induces an anti-self IgE response in a mammal.

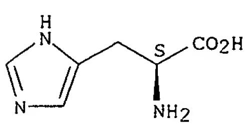
IT **26062-48-6**, Polyhistidine **26854-81-9**, Polyhistidine
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced vaccines comprising self IgE portion and non-self IgE portion for atopic allergy and infection)

RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

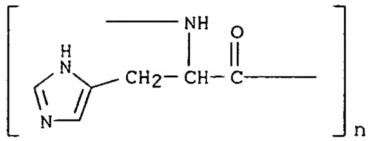
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



=> d bib abs hitstr l47 3

L47 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:145061 HCAPLUS
DN 132:204834
TI In vitro enzyme activity screen with substrate replacement
IN Pedersen, Henrik; Holder, Swen; Kjems, Jorgen; Lund, Mette Katrine
PA Novo Nordisk A/S, Den.
SO PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000011211	A1	20000302	WO 1999-DK441	19990817

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI DK 1998-1044 19980819
DK 1998-1106 19980902

AB A method for in vitro selection, from a library of catalyst mols., of a catalyst mol. of interest having a relatively more efficient specific catalytic activity, as compared to the rest of the catalyst mols. within said library, is disclosed. The in vitro selection method allows multiple catalytic activity turnovers (i.e. substrate to product conversions) by the catalyst mol. of interest before it is finally collected. The library of catalyst mols. comprises individual units C-XY-S (C = catalyst; X,Y = an exchange pair; S = substrate), which are converted to C-XY-P (P = product) by the catalytic activity of C. The C-XY-P unit is converted to the C-XY-S unit in the presence of Y-S. A characteristic of P allows isolation of a P-contg. substance which contains information allowing the unambiguous identification of the catalyst mol. which catalyzed the conversion C .fwdarw. P. Examples of XY exchange pairs include ligands and metal ions (such as ethylenediamine diacetate and Ca2+), complementary **nucleic acids**, and covalent bond-forming pairs such as boric acid and vicinal diols (e.g., sugars), esters and alcs., and thiols and dithiols. Thus, using the above method, enrichment of wild-type lipase in a background of excess, less active lipase variants was demonstrated using phage-displayed lipase and oligodeoxyribonucleotides as XY exchange pair.

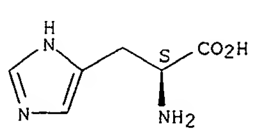
IT **26062-48-6D**, Poly-L-histidine, **complex** with iron
26854-81-9D, **complex** with iron
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(ethylenediamine and; in vitro enzyme activity screen with substrate replacement)

RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

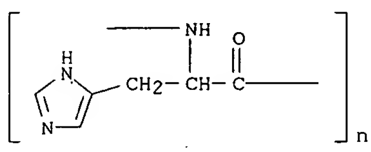
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI)
(CA INDEX NAME)



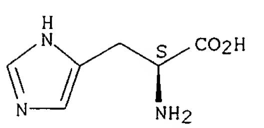
=> d bib abs hitstr l47 4

L47 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:27403 HCAPLUS
DN 132:156719
TI Design of imidazole-containing endosomolytic biopolymers for gene delivery
AU Pack, Daniel W.; Putnam, David; Langer, Robert
CS Department of Chemical Engineering, E25-342, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SO Biotechnol. Bioeng. (2000), 67(2), 217-223
CODEN: BIBIAU; ISSN: 0006-3592
PB John Wiley & Sons, Inc.
DT Journal
LA English
AB The development of safe and effective gene delivery agents poses a great challenge in the quest to make human gene therapy a reality. Cationic polymers represent one important class of materials for gene delivery, but to date they have shown only moderate efficiency. Improving the efficiency will require the design of new polymers incorporating optimized gene delivery properties. For example, inefficient release of the **DNA**/polymer **complex** from endocytic vesicles into the cytoplasm is one of the primary causes of poor gene delivery. Here the authors report the synthesis of a biocompatible, imidazole-contg. polymer designed to overcome this obstacle. **DNA**/polymer polyplexes incorporating this polymer were shown to have desirable physico-chem. properties for gene delivery and are essentially nontoxic. Using this system, mammalian cells in vitro were transfected in the absence of any exogenous endosomolytic agent such as chloroquine.
IT **26062-48-6P**, Polyhistidine **26854-81-9P**, Polyhistidine
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design of imidazole-contg. endosomolytic biopolymers for gene delivery)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

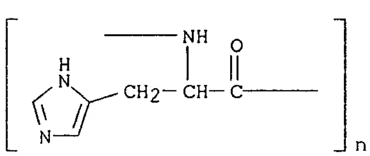
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RE.CNT 37
RE
(1) Abdallah, B; Hum Gene Ther 1996, V7, P1947 HCAPLUS
(4) Behr, J; Chimia 1997, V51, P34 HCAPLUS
(5) Boussif, O; Proc Natl Acad Sci 1995, V92, P7297 HCAPLUS

(6) Cheng, P; Hum Gene Ther 1996, V7, P275 HCAPLUS
(8) Cotten, M; Methods Enzymol 1993, V217, P618 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l47 5

L47 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:343 HCAPLUS
DN 132:61296
TI Method for transporting substances into eukaryotic cells and compartments thereof
IN Bertling, Wolf
PA November A.-G. Novus Medicatus Bertling Gesellschaft fuer Molekulare Medizin, Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	DE 19829005	A1	19991230	DE 1998-19829005	19980629
	DE 19829005	C2	20000831		
	WO 2000000224	A2	20000106	WO 1999-DE1805	19990619
	WO 2000000224	A3	20000413		

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

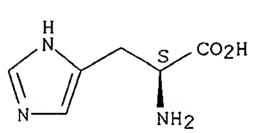
	EP 1007107	A2	20000614	EP 1999-939916	19990619

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI
PRAI DE 1998-19829005 19980629
WO 1999-DE1805 19990619
AB A method for prepn. of a vehicle to transport mol. substances such as **DNA**, RNA, PNA, proteins, and drugs into eukaryotic cell membranes, cytoplasm, or nuclei is disclosed. The mol. substance is **conjugated** to, assocd. with, or enclosed in a biopolymer. A modified viral protein, or a protein derived from a virus, which provides a targeting function is **conjugated** or assocd. with the biopolymer. Thus, empty His-tagged/non-His-tagged polyomavirus VP1 capsids were prepd. with Escherichia coli. Incubation with **oligonucleotides** provided a polyoma-like particle which was used to introduce the **oligonucleotide** into 3T3 cells.
IT **26062-48-6D**, Polyhistidine, **conjugates** with viral proteins **26854-81-9D**, Polyhistidine, **conjugates** with viral proteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (method for transporting substances into eukaryotic cells and compartments thereof)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

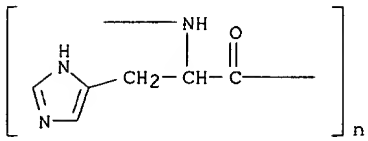
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RE.CNT 1
RE
(1) Anon; DE 19618797 A1 HCAPLUS

=> d bib abs hitstr 147 6

L47 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:810926 HCAPLUS
DN 132:50402
TI Polyamine telomers and compositions containing them useful for the transfer of active substances into a cell
PA Transgene S.A., Fr.
SO Eur. Pat. Appl., 36 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

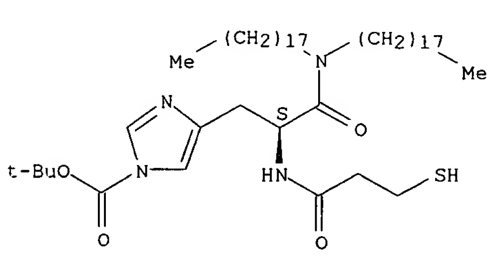
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 965583	A1	19991222	EP 1998-401471	19980615
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	EP 965584	A2	19991222	EP 1999-111504	19990614
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 9935043	A1	19991223	AU 1999-35043	19990615
	JP 2000143619	A2	20000526	JP 1999-168838	19990615

PRAI EP 1998-401471 19980615
AB Polyamine telomer compds. contg. S[CH2C[CONR1(CH2)xB]A]nH repeating units [A = H, C1-4 alkyl, or C5-7 aryl; n = 1-100; R1 = H, Me, Et, or (CH2)uB; x, u = 2-4; B = [NR3(CH2)y]zNR4R5 or [N+R7R3(CH2)y]zN+R4R5R6; y = 2-4; z = 0-6; R3-7 = H, C1-4 alkyl or C1-4 hydroxyalkyl] are manuf. for the title use. A typical telomer for the title use was manufd. by reaction of dioctadecylammonium hydrochloride with 3,3'-dithiopropanoyl chloride, reaction of the intermediate with Zn, telomerization of the resulting telogen with N-[2-(BOC)aminoethyl]acrylamide, and removal BOC from the resulting telomer.
IT **252870-27-2DP**, deprotected, **complexes** with **DNA** and DOPE
RL: IMF (Industrial manufacture); PREP (Preparation)
(polyamine telomers for the transfer of active substances into cells)
RN 252870-27-2 HCAPLUS
CN 1H-Imidazole-1-carboxylic acid, 4-[(2S)-3-(dioctadecylamino)-2-[(3-mercapto-1-oxopropyl)amino]-3-oxopropyl]-, 1,1-dimethylethyl ester, telomer with 1,1-dimethylethyl [2-[(1-oxo-2-propenyl)amino]ethyl]carbamate (9CI) (CA INDEX NAME)

CM 1

CRN 252870-15-8
CMF C50 H94 N4 O4 S

Absolute stereochemistry.

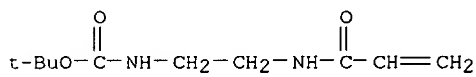


CM 2

CRN 252870-16-9
CMF (C10 H18 N2 O3)x
CCI PMS

CM 3

CRN 165196-44-1
CMF C10 H18 N2 O3

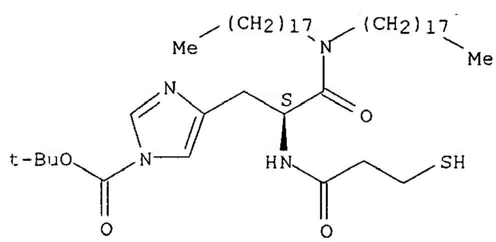


IT **252870-27-2P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation)
(protected telomer; polyamine telomers for the transfer of active substances into cells)
RN 252870-27-2 HCAPLUS
CN 1H-Imidazole-1-carboxylic acid, 4-[(2S)-3-(dioctadecylamino)-2-[(3-mercapto-1-oxopropyl)amino]-3-oxopropyl]-, 1,1-dimethylethyl ester, telomer with 1,1-dimethylethyl [2-[(1-oxo-2-propenyl)amino]ethyl]carbamate (9CI) (CA INDEX NAME)

CM 1

CRN 252870-15-8
CMF C50 H94 N4 O4 S

Absolute stereochemistry.

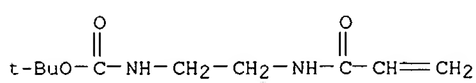


CM 2

CRN 252870-16-9
CMF (C10 H18 N2 O3)x
CCI PMS

CM 3

CRN 165196-44-1
CMF C10 H18 N2 O3



RE.CNT 4
RE
(1) Amersham International PLC; EP 0618191 A 1994
(2) Nippon Shokubai Kagaku Kogyo Co Ltd; JP 63-251409 A 1988
(3) Nippon Shokubai Kagaku Kogyo Co Ltd; JP 63-251409 A 1988
(4) Taisho Pharmaceutical Co Ltd; WO 9303005 A

=> d bib abs hitstr l47 7

L47 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:549169 HCAPLUS
DN 131:169282
TI Modified heat shock protein-antigenic peptide **complex**
IN Podack, Eckhard R.; Spielman, Julie; Yamazaki, Koichi
PA University of Miami, USA
SO PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9942121	A1	19990826	WO 1999-US3561	19990219

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

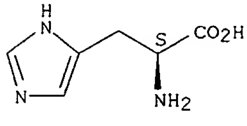
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 9927731	A1	19990906	AU 1999-27731	19990219

PRAI US 1998-75358 19980220
WO 1999-US3561 19990219
AB The present invention relates to methods for purifying immunogenic, prophylactically and therapeutically effective **complexes** of modified heat shock proteins noncovalently assocd. with antigenic peptides of cancer or infected cells. The claimed methods comprise the constructing of a nucleotide sequence encoding a secretable modified heat shock protein, expressing the sequence in an appropriate host cell, recovering the immunogenic **complexes** from the cell culture and the cells, and purifying the immunogenic **complexes** by affinity chromatog. Large amts. of such immunogenic **complexes** can be obtained by large-scale culturing of host cells contg. the genetic sequence. The **complexes** can be used as a vaccine to elicit specific immune responses against cancer or infected cells, and to treat or prevent cancer or infectious diseases. Thus, modified gp96-IgG1 fusion protein was prepd. by mol. cloning, and protective effect of vaccination with cells expressing the modified fusion protein was tested.
IT **26062-48-6**, Polyhistidine **26854-81-9**, Polyhistidine
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide tag; modified heat shock protein-antigenic peptide **complex** as vaccine and for treating and preventing cancer or infectious disease)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

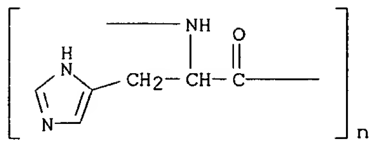
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RE.CNT 4
RE

(1) Anon; Clonetech Catalogue 1997-1998, P153
(2) Mount Sinai School of Medicine of The City University of New York; WO 95/24923 A2 1995 HCAPLUS
(3) Mount Sinai School of Medicine of The City University of New York; WO 96/10411 A1 1996 HCAPLUS
(4) Srivastava, P; Advances in Cancer Research 1993, V62, P154

=> d bib abs hitstr l47 8

L47 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:549141 HCAPLUS
DN 131:175080
TI Cell delivery compositions containing biocompatible endosomolytic agents
IN Langer, Robert S.; Putnam, David A.; Pack, Daniel W.
PA Massachusetts Institute of Technology, USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

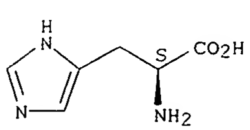
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9942091	A2	19990826	WO 1999-US3294	19990216
	WO 9942091	A3	20000120		

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 1998-75272 19980219
AB The present invention provides improved cell delivery compns. In particular, the invention provides biocompatible endosomolytic agents. In a preferred embodiment, the endosomolytic agents are also biodegradable and can be broken down within cells into components that the cells can either reuse or dispose of. Preferred endosomolytic agents include cationic polymers, particularly those comprised of biomols., such as histidine, polyhistidine, polylysine or any combination thereof. Other exemplary endosomolytic agents include, but are not limited to, other imidazole contg. compds. such as vinylimidazole and histamine. More particularly preferred are those agents having multiple proton acceptor sites and acting as a "proton sponge", disrupting the endosome by osmolytic action. In preferred embodiments, the endosomolytic agent comprises a plurality of proton acceptor sites having pKas within the range of 4 to 7, which endosomal lysing component is polycationic at pH 4. The present invention also contemplates the use of these endosomolytic agents as delivery agents by **complexation** with the desired compd. to be delivered. Thus, the present invention also acts as a cell delivery system comprising an endosomolytic agent, a delivery agent, and a compd. to be delivered. Examples were given for prepn. of gluconic acid-modified polyhistidine and delivery of **nucleic acid** encoding .beta.-galactosidase from a gluconylated-polyhistidine/transferrin-polylysine compn.
IT **26062-48-6D**, Poly(L-histidine), gluconic acid-modified
26854-81-9D, gluconic acid-modified
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cell delivery compns. contg. biocompatible endosomolytic agents)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

CM 1

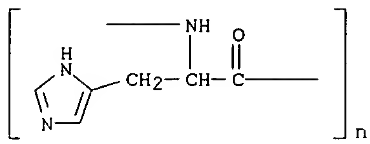
CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI)

(CA INDEX NAME)



=> d bib abs hitstr 147 9

STN - COLUMBUS WILL BE TERMINATING ALL SESSIONS IN 10 MINUTES.
PLEASE SAVE DESIRED INFORMATION AND LOGOFF.

L47 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:189279 HCAPLUS
DN 130:220168
TI Processes and kits for mass spectrometric determination of polypeptides
IN Little, Daniel; Koster, Hubert; Higgins, G. Scott; Lough, David
PA Sequenom, Inc., USA
SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9912040	A2	19990311	WO 1998-US18311	19980902
	WO 9912040	A3	19990902		

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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 9891298	A1	19990322	AU 1998-91298	19980902
	EP 1010008	A2	20000621	EP 1998-943528	19980902

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

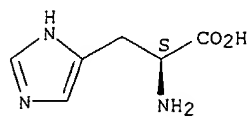
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	DE 19882657	T	20000824	DE 1998-19882657	19980902
	NO 2000001043	A	20000502	NO 2000-1043	20000301

PRAI US 1997-922201 19970902
WO 1998-US18311 19980902
AB A process for detg. the identity of a target polypeptide using mass spectroscopy is provided. Depending on the target polypeptide to be identified, a process as disclosed can be used, for example, to diagnose a genetic disease or chromosomal abnormality, a predisposition to a disease or condition, or infection by a pathogenic organism; or for detg. identity or heredity. Kits for performing the disclosed processes also are provided. Human genomic **DNA**, extd. from blood of patients with spinal cerebellar ataxia 1, was amplified by PCR using forward and reverse primers contg. the T7 promoter sequence and a sequence encoding the His-6 tag peptide, resp., and hybridizing to sequences located on either side of the CAG trinucleotide repeat. The amplified **DNA** was subjected to in vitro transcription and translation, and the target polypeptides were isolated on a nickel chromatog. column. Mass spectrometric anal. of the polypeptides indicated that these peptides had mol. masses of 8238.8, 8865.4, and 8993.6 Da, corresponding to 10, 15, or 16 CAG (Asn) repeats. The polypeptide encoded by the **nucleic acid** from the fourth patient, having and unknown no. of trinucleotide repeats, had a mol. mass of 8224.8 Da. While this value does not correspond exactly with a unit no. of repeats (10 is the closest), it is consistent with detection of a point mutation; i.e. the -14 Da shift for this polypeptide corresponds to an Ala to Gly mutation due to a C to G mutation in one of the repeats.
IT **26062-48-6**, Polyhistidine
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(as tag peptide, target polypeptide contg.; processes and kits for mass spectrometric detn. of polypeptides)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



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L47  ANSWER 10 OF 23  HCAPLUS  COPYRIGHT 2000 ACS
AN   1999:133618  HCAPLUS
DN   130:187175
TI   Conjugates targeted to the interleukin-2 receptor
IN   Prakash, Ramesh K.
PA   Theratech, Inc., USA
SO   PCT Int. Appl., 53 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
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     WO 9907324        A3   19990415
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             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
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         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
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     EP 1011705        A2   20000628       EP 1998-939226   19980805
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     ZA 9807181        A    19990323      ZA 1998-7181     19980811
PRAI US 1997-914042   19970805
     WO 1998-US16290  19980805
AB   A compn. for intracellular delivery of a chem. agent into an
     interleukin-2-receptor-bearing cell, e.g. an activated T cell, includes a
     chem. agent and at least two copies of an interleukin-2-receptor-binding
     and endocytosis-inducing ligand coupled to a water sol. polymer.  The
     ligand binds to a receptor on the interleukin-2-receptor-bearing cell and
     elicits endocytosis of the compn.  The compn. also optionally includes a
     spacer for coupling the chem. agent and the ligand to the polymer.  Chem.
     agents can include cytotoxins, transforming nucleic
     acids, gene regulators, labels, antigens, drugs, and the like.  A
     preferred water sol. polymer is polyalkylene oxide, such as polyethylene
     glycol and polyethylene oxide, and activated derivs. thereof.  The compn.
     can further comprise a carrier such as another water sol. polymer,
     liposome, or particulate.  Methods of using these compns. for delivering a
     chem. agent in vivo or in vitro are also disclosed.
IT   220680-36-4P 220680-39-7P 220680-40-0P
     220680-41-1P 220680-42-2P 220680-43-3P
     220680-44-4P
     RL: BAC (Biological activity or effector, except adverse); PNU
     (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological
     study); PREP (Preparation); USES (Uses)
        (conjugates targeted to the interleukin-2 receptor)
RN   220680-36-4  HCAPLUS
CN   Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-, 1-ether with
     (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-
     10-[[2,3,6-trideoxy-3-[[N-(2-hydroxyethyl)glycyl-L-leucyl-L-glutaminyl-L-
     histidyl-L-leucyl-L-phenylalanyl-L-leucylglycyl]amino]-.alpha.-L-lyxo-
     hexopyranosyl]oxy]-5,12-naphthacenedione (9CI)  (CA INDEX NAME)
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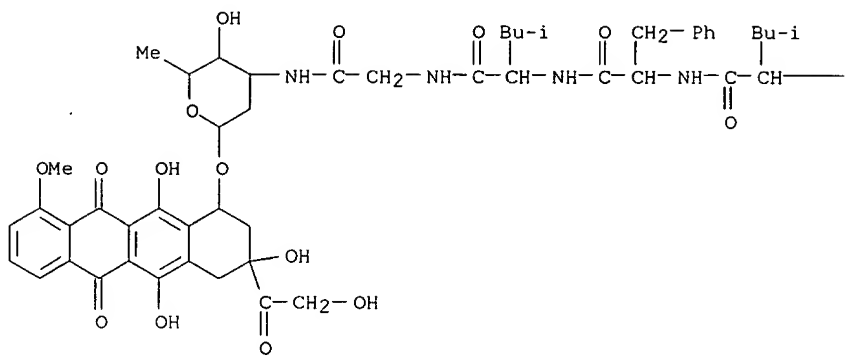

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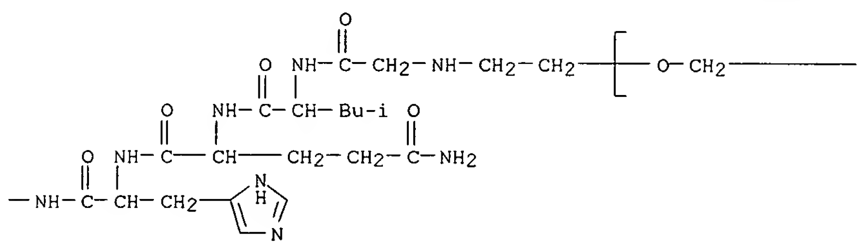

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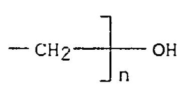

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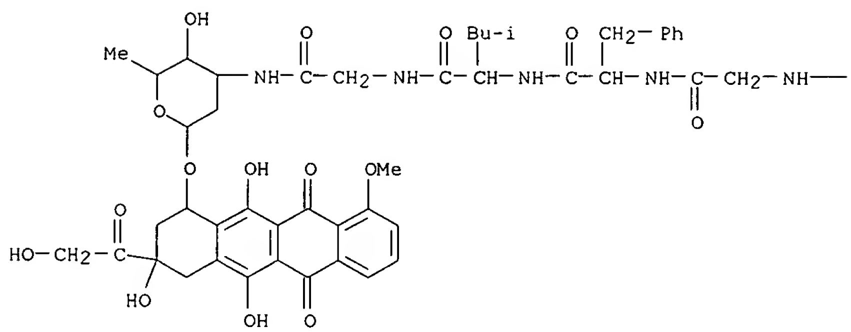

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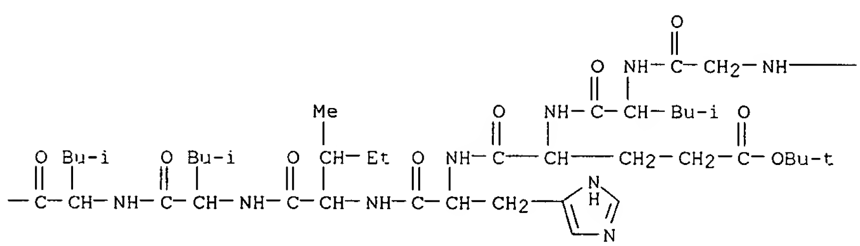

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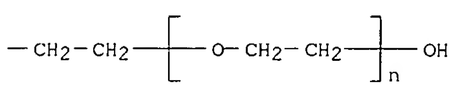

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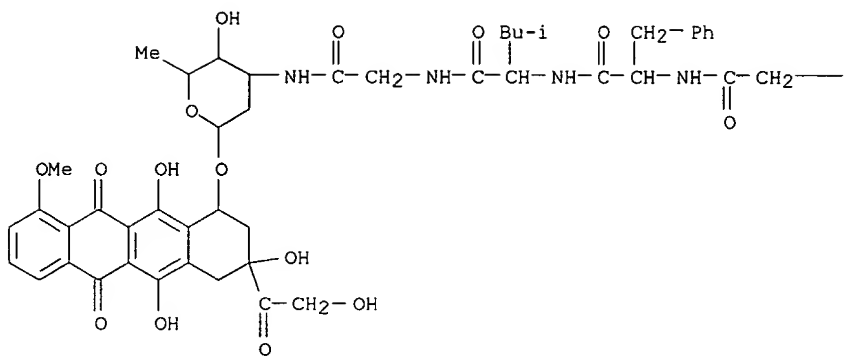

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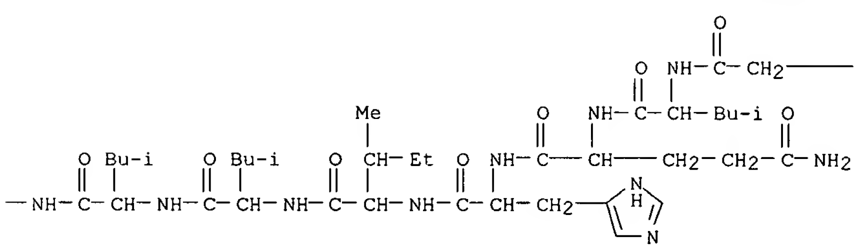

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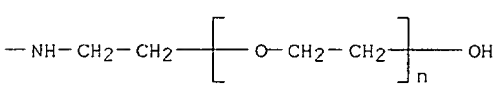

RN 220680-41-1 HCAPLUS

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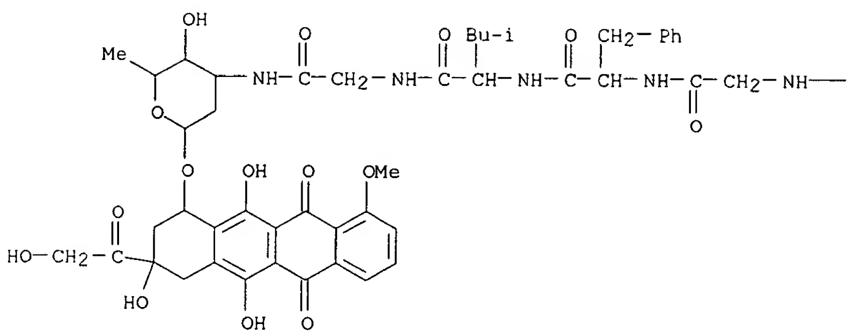

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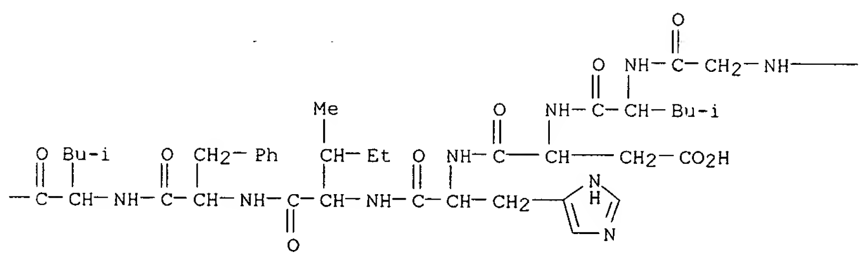

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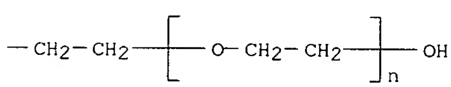

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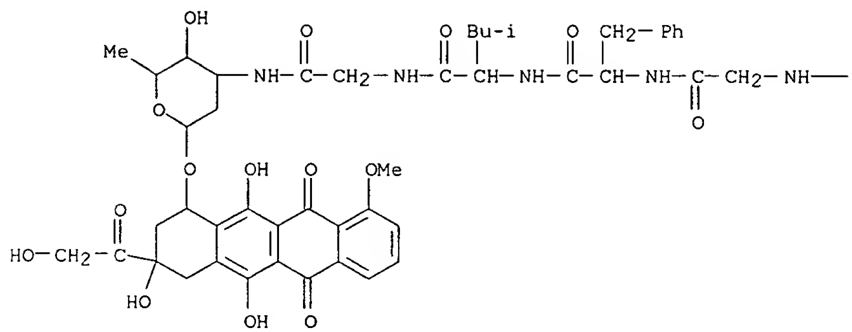

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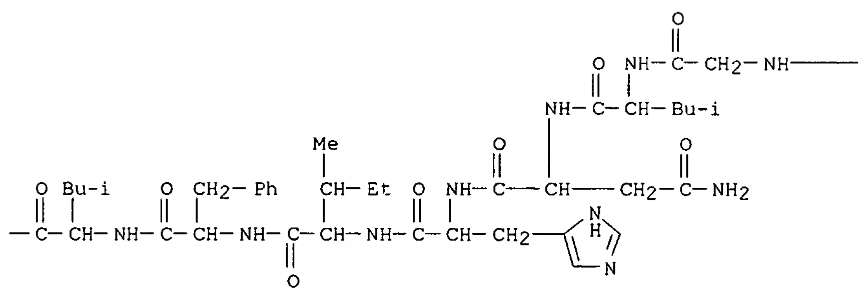

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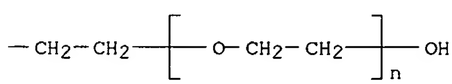

RN 220680-43-3 HCAPLUS

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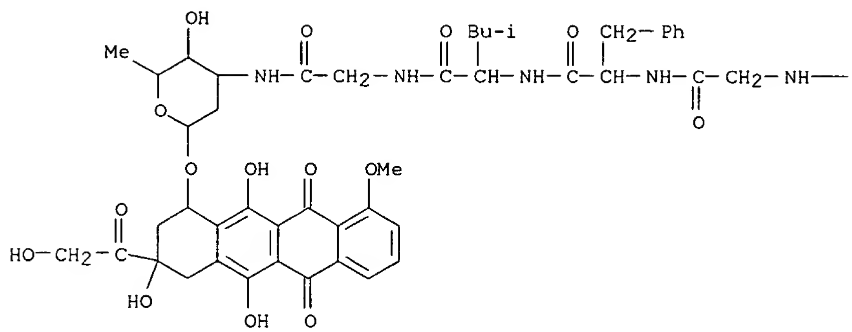

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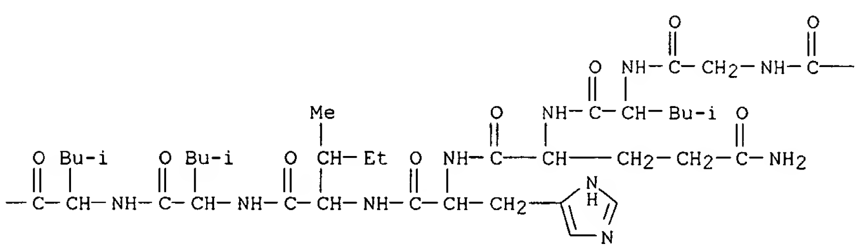

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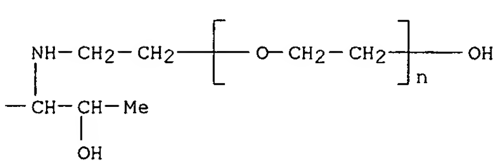

RN 220680-44-4 HCAPLUS

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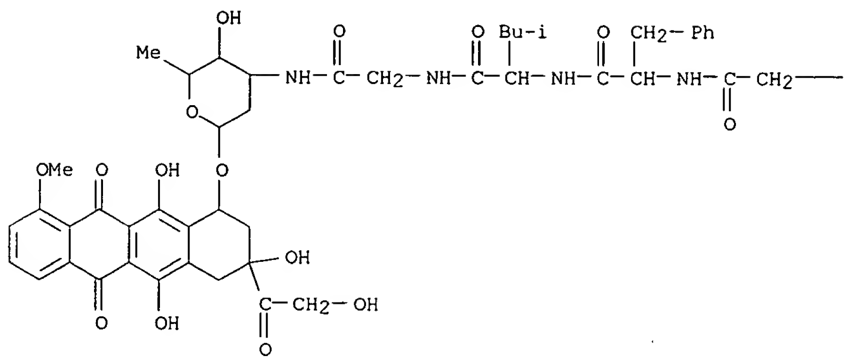

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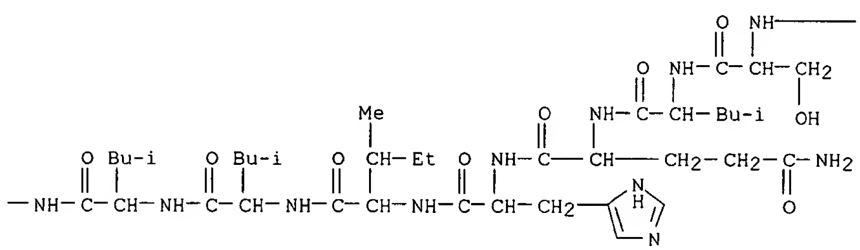

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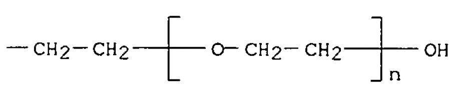

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L47 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:48050 HCAPLUS
DN 130:71597
TI Polymer composition for controlled release of active ingredients in response to pH
IN Mashelkar, Raghunathy Anant; Kulkarni, Mohan Gopalkishna; Karmalkar, Rohini Nitin
PA Council of Scientific and Industrial Research, India
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

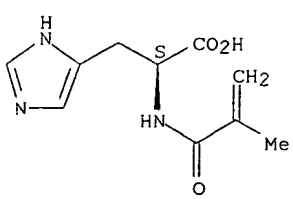
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5851546	A	19981222	US 1996-615431	19960314
PRAI	IN 1995-DE1095	19950614			

AB The present invention provides a polymer for the controlled release of a pendent chain linked active ingredient, and a process for the prepn. of such a polymer for the controlled release of an active ingredient in response to pH. The process involves selecting a vinyl monomer to which the active ingredient mol. is covalently linked through a pendent group, and selecting monomers bearing catalytic groups. The active ingredient-bearing monomer and the catalytic group-contg. monomer are brought in juxtaposition either by complexation or mol. imprinting, and then polymd. with a hydrophilic monomer and crosslinker under an inert atm. with a suitable polymn. initiator. P-nitrophenyl p-vinylbenzoate was prepd. and polymd. with 1-vinylimidazole and 2-hydroxyethyl methacrylate and it was obsd. that in 60 h 50% p-nitrophenol was release from this polymer.
IT **182815-34-5P 208771-82-8P 218275-27-5P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(controlled release of active ingredient from vinyl polymers)
RN 182815-34-5 HCAPLUS
CN L-Histidine, N-(2-methyl-1-oxo-2-propenyl)-, polymer with 2-hydroxyethyl 2-methyl-2-propenoate and 4-nitrophenyl 4-ethenylbenzoate (9CI) (CA INDEX NAME)

CM 1

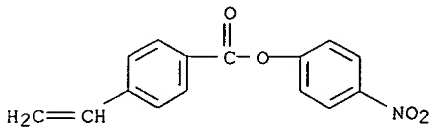
CRN 13282-13-8
CMF C10 H13 N3 O3
CDES 5:L

Absolute stereochemistry.



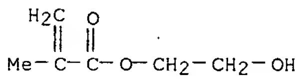
CM 2

CRN 3302-17-8
CMF C15 H11 N O4



CM 3

CRN 868-77-9
CMF C6 H10 O3

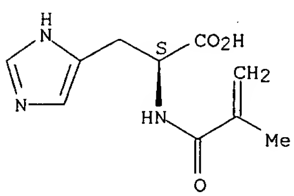


RN 208771-82-8 HCAPLUS
CN L-Histidine, N-(2-methyl-1-oxo-2-propenyl)-, polymer with 2-hydroxyethyl 2-methyl-2-propenoate and 2-methyl-2-propenoic acid (9CI) (CA INDEX NAME)

CM 1

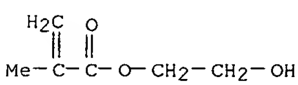
CRN 13282-13-8
CMF C10 H13 N3 O3
CDES 5:L

Absolute stereochemistry.



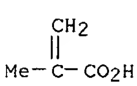
CM 2

CRN 868-77-9
CMF C6 H10 O3



CM 3

CRN 79-41-4
CMF C4 H6 O2

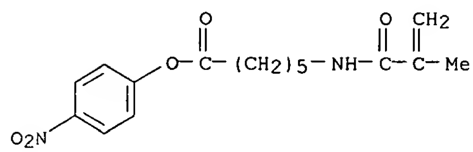


RN 218275-27-5 HCAPLUS
CN L-Histidine, N-(2-methyl-1-oxo-2-propenyl)-, polymer with 1,2-ethanediyl bis(2-methyl-2-propenoate), 2-hydroxyethyl 2-methyl-2-propenoate and

4-nitrophenyl 6-[(2-methyl-1-oxo-2-propenyl)amino]hexanoate (9CI) (CA INDEX NAME)

CM 1

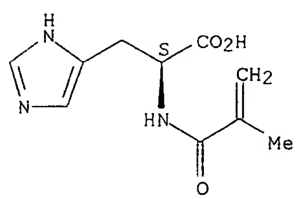
CRN 57950-59-1
CMF C16 H20 N2 O5



CM 2

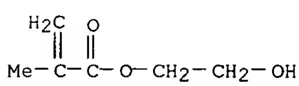
CRN 13282-13-8
CMF C10 H13 N3 O3
CDES 5:L

Absolute stereochemistry.



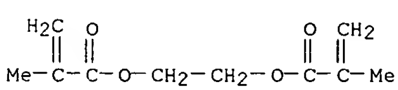
CM 3

CRN 868-77-9
CMF C6 H10 O3



CM 4

CRN 97-90-5
CMF C10 H14 O4



RE.CNT 13
RE
(3) Bawa; US 4931279 1990 HCAPLUS
(5) Fitch, R; J Colloid Interface Sci 1979, V71, P107 HCAPLUS
(6) Mueller; US 4177056 1979 HCAPLUS
(9) Shah, S; J Appl Polym Sci 1990, V41, P2437 HCAPLUS
(11) Steckler; US 4071508 1978 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

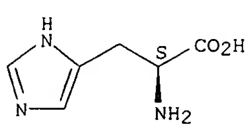
=> d bib abs hitstr 147 12

L47 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:37433 HCAPLUS
DN 130:193316
TI Physicochemical and functional comparison of Xenopus laevis nucleoplasmin obtained from oocytes and from overexpression in bacteria
AU Saperas, Nuria; Chiva, Manel; Aligue, Rosa; Itoh, Toru; Katagiri, Chiaki; Subirana, Juan Antonio; Ausio, Juan
CS Department d'Enginyeria Quimica, E.T.S.E.I.B., Barcelona, E-08028, Spain
SO Arch. Biochem. Biophys. (1999), 361(1), 135-141
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
AB We compare the physicochem. and functional characteristics of nucleoplasmin obtained from Xenopus laevis oocytes and by bacterial overexpression of a **plasmid** contg. the nucleoplasmin gene. The comparison shows that, while the secondary structure of the protein is not affected by the method used to obtain this protein, the bacterial expressed form exhibits a marked tendency to form large aggregates and an impaired ability to displace protamines from sperm nuclei. These results add a word of caution to the indiscriminate use, in functional or structural (crystallog.) studies, of bacterially overproduced proteins that have been end-terminally tagged with polyhistidine. (c) 1999 Academic Press.
IT **26062-48-6D**, Poly L-histidine, **conjugates** with nucleoplasmin
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(physicochem. and functional comparison of Xenopus laevis nucleoplasmin obtained from oocytes and from overexpression in bacteria)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RE.CNT 42
RE

(1) Andersson, S; Microbiol Rev 1990, V54, P198 HCAPLUS
(3) Beaudette, N; Biochemistry 1981, V20, P6526 HCAPLUS
(4) Bradbury, E; Eur J Biochem 1975, V52, P605 HCAPLUS
(6) Chen, H; EMBO J 1994, V13, P380 HCAPLUS
(8) Chou, P; Biochemistry 1974, V13, P211 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l47 13

L47 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:682530 HCAPLUS
DN 129:299047
TI Human secreted F-spondin homolog and its cDNA and diagnosis of prostate cancer
IN Sheppard, Paul O.
PA Zymogenetics, Inc., USA
SO PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9845442	A2	19981015	WO 1998-US7117	19980410
	WO 9845442	A3	19990114		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 9869613	A1	19981030	AU 1998-69613	19980410

PRAI US 1997-43421 19970410
US 1997-49288 19970611
WO 1998-US7117 19980410

AB The present invention relates to a secreted protein expressed at very high level in prostate tissue and **polynucleotides** encoding the same. This protein, called Zsig25, contains an N-terminal domain with homol. to rat floor plate F-spondin and a C-terminal sequence which appears to be a sinle thrombospondin type 1 domain. Zsig25 is believed to be adhesion-modulating and may be used for diagnosis of prostate adenocarcinoma or for sorting cancerous from non-cancerous cells. The present invention also includes antibodies to the Zsig25. The Zsig25 gene was mapped to human chromosome 4p16.3, the region assocd. with Wolf-Hirschhorn syndrome. Zsig25 with an N-terminal FLAG peptide was produced with BHK 570 cells transformed with expression **vector** zSIG25NF/pZP9. An adenovirus expression **vector** was also prepd. The FLAG-Zsig25 protein stimulated proliferation of BaF3 and CA-1 cell lines, an interleukin 3-dependent pre-lymphoid cell line derived from bone marrow and another interleukin 3-dependent cell line obtained from lymph nodes of a mouse with B-cell lymphoma.

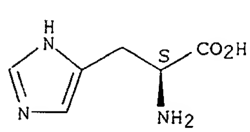
IT **26062-48-6**, Polyhistidine **26854-81-9**, Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]]
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(fusion proteins with Zsig25; human secreted F-spondin homolog and its cDNA and diagnosis of prostate cancer)

RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

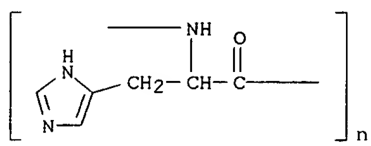
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI)
(CA INDEX NAME)



=> d bib abs hitstr l47 14

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L47  ANSWER 14 OF 23  HCAPLUS  COPYRIGHT 2000 ACS
AN   1998:604833  HCAPLUS
DN   129:215712
TI   Chelating immunostimulating complexes
IN   MacFarlan, Roderick Ian; Malliaros, Jim
PA   Csl Ltd., Australia
SO   PCT Int. Appl., 78 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
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PI   WO 9836772        A1   19980827      WO 1998-AU80     19980213
         W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
            DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG,
            KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
            NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
            UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
            FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
            GA, GN, ML, MR, NE, SN, TD, TG
     AU 9858488        A1   19980909      AU 1998-58488    19980213
     AU 720855         B2   20000615
     EP 986399         A1   20000322      EP 1998-901888   19980213
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, FI
     ZA 9801281        A    19981119      ZA 1998-1281     19980217
PRAI AU 1997-5178      19970219
     WO 1998-AU80      19980213
AB   An immunostimulating complex matrix comprising a saponin prepn.,
     a sterol and a phospholipid, the matrix further comprising a
     metal-chelating moiety capable of binding a protein or polypeptide having
     at least one chelating amino acid sequence in the presence of metal ions.
     An immunogenic immunostimulating complex which comprises this
     matrix and an immunogenic protein or polypeptide having at least one
     chelating amino acid sequence, the protein or polypeptide being bound to
     the matrix in the presence of metal ions.  ISCOM comprising ISCOPREP703 (a
     Quillaja saponin mixt.), cholesterol, and DPPC was prepd. and used as
     adjuvant for vaccine contg. fusion protein of HPV-16 E6 and E7 and
     hexahistidine sequence, and for vaccine contg. recombinant family C
     protein of Helicobacter pylori with hexahistidine sequence.
IT   26062-48-6, Polyhistidine 26854-81-9, Polyhistidine
     RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (chelating immunostimulating complex matrix comprising
        saponin and sterol and phospholipid as immune adjuvant for polypeptide
        vaccines)
RN   26062-48-6  HCAPLUS
CN   L-Histidine, homopolymer (9CI)  (CA INDEX NAME)

     CM   1

     CRN  71-00-1
     CMF  C6 H9 N3 O2

Absolute stereochemistry.  Rotation (-).
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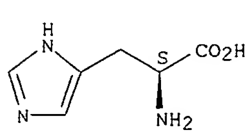

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RN   26854-81-9  HCAPLUS
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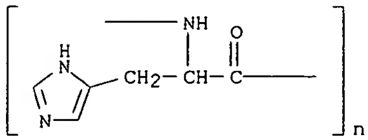
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI)
(CA INDEX NAME)



=> d bib abs hitstr l47 15

L47 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:293610 HCAPLUS
DN 128:304799
TI Recombinant soluble Tie2 receptor as angiogenesis inhibitor and antitumor agent
IN Peters, Kevin G.; Lin, Charles; Rao, Prema S.; Dewhirst, Mark W.
PA Duke University, USA
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

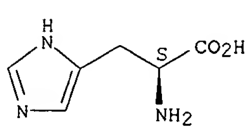
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9818914	A1	19980507	WO 1997-US19597	19971031
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9851540	A1	19980522	AU 1998-51540	19971031
PRAI	US 1996-29407	19961031			
	WO 1997-US19597	19971031			

AB The present invention relates to a sol. Tie2 receptor and its use as an antiangiogenic agent. The ExTek.6His baculovirus **vector** was constructed to produce a protein with the extracellular domain of the Tie2/Tek protein attached to (His)6. The purified ExTek.6His protein inhibited tumor vascularization, but did not affect tumor cell proliferation or viability. The AdExTek adenoviral **vector** expressing the extracellular domain of the Tie2/Tek protein was used for gene transfer to mice implanted with tumor cell lines. AdExTek inhibited tumor growth rate and suppressed metastasis. Other vascular endothelial receptor domain-contg. recombinant fusion proteins (ExFlk.6His for the vascular endothelial growth factor receptor and ExFms.6His for colony-stimulating factor 1 receptor) were also produced and studied for their effects on angiogenic response of tumors.
IT **26062-48-6P**, Polyhistidine **26854-81-9P**, Polyhistidine
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Tie2 receptor extracellular domain in chimeric, sol. protein used as angiogenesis inhibitor for tumors)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

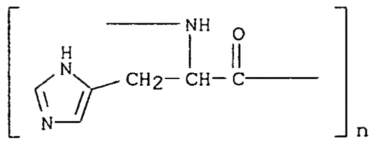
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



=> d bib abs hitstr l47 16

L47 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:263166 HCAPLUS
DN 128:326502
TI Drug delivery compositions containing drug **complexes** with cationic polymers
IN Illum, Lisbeth
PA Danbiosyst UK Limited, UK
SO U.S., 8 pp. Cont.-in-part of U.S. 5,554,388.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5744166	A	19980428	US 1995-576877	19951221
	WO 9009780	A1	19900907	WO 1990-GB291	19900223
	W: CA, JP, NO, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	US 5554388	A	19960910	US 1993-167611	19931214

PRAI EP 1989-45370 19890225
WO 1990-GB291 19900223
US 1991-743328 19910820
US 1993-167611 19931214
GB 1989-4370 19890225

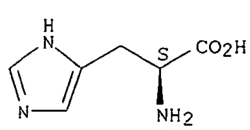
AB Compns. for delivery of pharmacol. active agents and methods for their administration are provided. In one embodiment, the compns. include a **complex** of a polycationic polymer and a pharmacol. active agent in a pharmaceutically acceptable carrier. The compns. permit transport of pharmacol. active compds. across mucosal membranes for systemic delivery. The polycationic polymer may be, for example, a polycationic carbohydrate such as a chitosan or a chitosan salt or deriv. The therapeutic agent can be a vaccine or a **nucleic acid,** such as a gene or antisense **oligonucleotide**. The compn. may be provided in different forms such as solns., dispersions, powders, and microspheres. An insulin soln. was prepd. in a phosphate buffer (pH 7.3) to give a concn. of 167 IU/mL and DEAE-dextran was added to give concns. of 1, 5, or 10 % wt./vol. The solns. were administered nasally to rats at 16.7 IU/kg and blood samples were collected. The results showed that insulin given intranasally as a simple phosphate buffer soln. did not significantly lower the blood glucose level, whereas the addn. of the DEAE-dextran caused fast and significant decreases in blood glucose levels.

IT **26062-48-6,** Polyhistidine **26854-81-9,** Polyhistidine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polycationic polymer **complexes** with pharmacol. active agent for improved delivery across mucosa)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

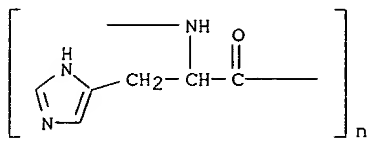
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



=> d bib abs hitstr l47 17

L47 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:465141 HCAPLUS
DN 127:78232
TI Luminescent probes for protein detection
IN Patton, Wayne F.; Shepro, David
PA Trustees of Boston University, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9720213	A1	19970605	WO 1996-US18575	19961119

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 9710559	A1	19970619	AU 1997-10559	19961119
	EP 807254	A1	19971119	EP 1996-941407	19961119

R: CH, DE, FR, GB, LI, SE

PRAI US 1995-564953 19951130
WO 1996-US18575 19961119

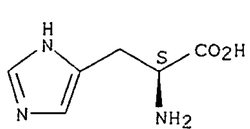
AB The invention relates to novel chem. **complexes** and compns. comprising lanthanide chelates. Methods for detecting, quantifying, and isolating targets are described, including immunoassays. Such methods comprise contacting the target with a lanthanide chelate, illuminating the resulting lanthanide-chelate-target **complex** with electromagnetic radiation, and detecting emitted phosphorescence of the lanthanide, thereby identifying the presence and location of the **complex**. The chelate comprises a first domain that binds to the lanthanide, a second domain that specifically and reversibly binds to the target, and a third domain that absorbs UV light. Lanthanide chelates can be safely and completely eluted from the target and the target isolated and utilized for addnl. applications. These lanthanide chelates or lanthanide-chelate-target **complexes** can be used in kits for the rapid, specific and sensitive detection of targets from samples obtained from patients, animals, cultures, or the environment.

IT **26062-48-6**, Poly-L-histidine **26854-81-9**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(luminescent probes for protein detection)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

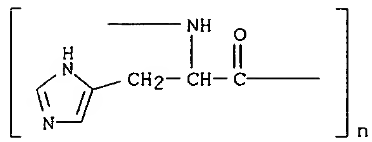
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



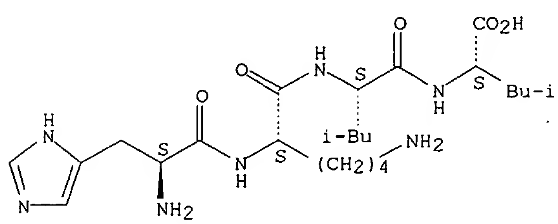
=> d bib abs hitstr 147 18

L47 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:386861 HCAPLUS
DN 125:80354
TI Computer design, synthesis and hydrolytic activity of peptidic artificial ribonucleases
AU Lorthioir, O.; Truffert, J. C.; Sy, D.; Barbier, B.; Lelievre, D.; Brack, A.
CS Cent. Biophysique Moleculaire, C.N.R.S. U.P.R., Orleans, 45071, Fr.
SO Protein Pept. Lett. (1996), 3(3), 153-160
CODEN: PPELEN; ISSN: 0929-8665
DT Journal
LA English
AB An RNA cleaving catalyst combined to an antisense **DNA** may represent a new approach for gene targeted therapy. As cleaving agents, we used basic polypeptides under the .beta.-sheet or .alpha.-helix conformations. Mol. modeling studies were used to design a second generation of artificial RNases, taking into account the three-dimensional arrangement of functional groups in the peptide/RNA **complexes**. Such computer aid in rational design processes appears as an original and promising approach.
IT **178694-76-3P**
RL: PNU (Preparation, unclassified); PRP (Properties); PREP (Preparation)
(computer design, synthesis and hydrolytic activity of peptidic artificial RNases)
RN 178694-76-3 HCAPLUS
CN L-Leucine, N-[N-(N2-L-histidyl-L-lysyl)-L-leucyl]-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 178694-75-2
CMF C24 H43 N7 O5
CDES 5:ALL,L

Absolute stereochemistry.



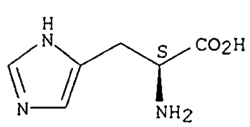
=> d bib abs hitstr l47 19

L47 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:194836 HCAPLUS
DN 116:194836
TI Conformation-controlled hydrolysis of polyribonucleotides by sequential basic polypeptides
AU Barbier, Bernard; Brack, Andre
CS Cent. Biophys. Mol., CNRS, Orleans, 45071, Fr.
SO J. Am. Chem. Soc. (1992), 114(9), 3511-15
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
AB Polycationic polypeptides contg. basic and hydrophobic amino acids strongly accelerate the hydrolysis of oligoribonucleotides. Aspects of the **oligonucleotide**-polypeptide interaction, as well as the relationship among amino acid compn., polypeptide conformation, and the hydrolytic effect were examd. To be active, the polypeptides must present a regular distribution in space of basic groups (.beta.-sheet or .alpha.-helix). A tentative model involving an alignment of the **polynucleotide** chain between two parallel rows of pos. charges is given. The exptl. data for the base-induced hydrolysis are consistent with a mechanism involving two basic amino acid side chains.
IT **26062-48-6**, Histidine homopolymer **26854-81-9**, Poly(histidine), SRU
RL: CAT (Catalyst use); USES (Uses)
(inactive catalyst, for hydrolysis of oligoribonucleotides)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

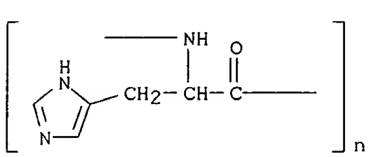
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



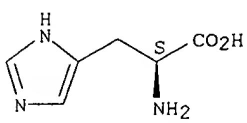
=> d bib abs hitstr 147 20

L47 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:81074 HCAPLUS
DN 106:81074
TI Mechanism studies of Coomassie Blue and silver staining of proteins
AU De Moreno, Miriam R.; Smith, Jean F.; Smith, Robert V.
CS Coll. Pharm., Univ. Texas, Austin, TX, 78712-1074, USA
SO J. Pharm. Sci. (1986), 75(9), 907-11
CODEN: JPMSAE; ISSN: 0022-3549
DT Journal
LA English
AB A relatively high **complexation** affinity has been found for Coomassie Blue G-250 and the following amino acids: arginine; tyrosine; lysine; and histidine. A linear relationship was obsd. between log molar absorptivity and log mol. wt. of 52 and 69 proteins, polypeptides, and di- and tripeptides that were allowed to react with Coomassie Blue G-250 in soln. The soln. **complexation** results were used in a study of the detection of the following model proteins: bovine serum albumin, lysozyme, recombinant **DNA** derived human insulin, and calmodulin. Interactions between Coomassie Blue stained gels and Ag detection reagents were detd. and used as the basis for studies of enhanced sensitivity of detection of electrophoretically developed proteins. Sensitivity enhancements of up to 8-fold were obsd. when various sulfonic acid dye **complexed** proteins were detected with Ag reagents vs. the use of Ag reagents alone. A site-directed nucleation of Ag caused by the protein **complexed** sulfonic acid dyes is proposed as a mechanism for the obsd. enhancements.
IT **26062-48-6**, Polyhistidine **26854-81-9**, Polyhistidine
RL: ANST (Analytical study)
(**complexation** of, with Coomassie Blue G-250, in soln.)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

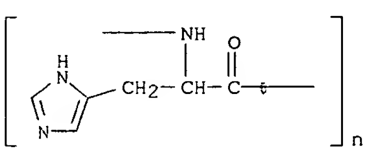
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



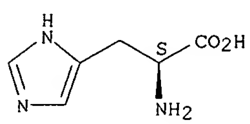
=> d bib abs hitstr l47 21

L47 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1981:169700 HCAPLUS
DN 94:169700
TI Conformation of **DNA** in **complexes** with amino acids and peptides
AU Pohle, W.; Fritzsche, H.; Richter, M.
CS Cent. Inst. Microbiol. Exp. Ther., DAW, Jena, DDR-6900, Ger. Dem. Rep.
SO Stud. Biophys. (1980), 81(2-3), 127-8
CODEN: STBIBN; ISSN: 0081-6337
DT Journal
LA English
AB Ligand-induced conformational changes in **DNA complexed** with amino acids, oligopeptides, and homopolypeptides (as protein model substances) as well as with small neutral ligands was studied by CD in relation to relative humidity. In **DNA complexes** with protein models, the common B and A forms of **DNA** were not obsd. At high humidity, the B* form described by J. Liquier, et al. (1975) is obsd. instead of the B form. At medium and low relative humidity, .gtoreq.2 different forms, the A form and 1 of the subforms of the B family, are obsd. As the ligand concn. in the **complex** increases, the B-A transition inhibition becomes stronger. The loss of conformational flexibility of **DNA** on **complexation** with protein models may play a role in the functional and regulatory aspects of **DNA**-protein interactions in vivo.
IT **26062-48-6D, DNA complex 26854-81-9D , DNA complex**
RL: PRP (Properties)
(conformation of, humidity in relation to)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

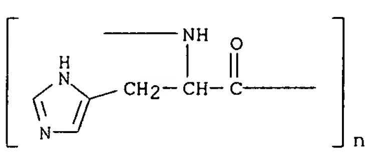
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



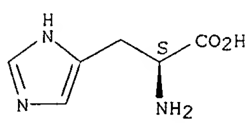
=> d bib abs hitstr 147 22

L47 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:175375 HCAPLUS
DN 84:175375
TI Large scale molecular organization in aggregates of **DNA** -poly-L-histidine association
AU Brini, M'Hamed; Bourgoin, Daniel
CS Dep. Rech. Phys., Univ. Pierre et Marie Curie, Paris, Fr.
SO C. R. Hebd. Seances Acad. Sci., Ser. D (1976), 282(9), 929-31
CODEN: CHDDAT
DT Journal
LA French
AB The aggregation state of the assocn. of poly-L-histidine with **DNA** depended on the saline concn. of the mixt. and on the degree of polymn. of the polypeptide. The CD of **DNA** assocd. with polyhistidine was very different from that of **DNA** alone and depended on the manner in which the mixt. was prepd. These large changes in the spectrum were attributed to a differnece in the large scale mol. organization of the aggregated particles.
IT **26062-48-6**
RL: BIOL (Biological study)
(CD of)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



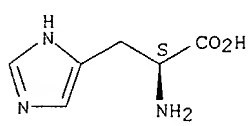
=> d bib abs hitstr 147 23

L47 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:146347 HCAPLUS
DN 84:146347
TI Conformation and reactivity of **DNA** in the **complex** with proteins. III. Helix-coil transition and conformational studies of model **complexes** of **DNA**'s with poly-L-histidine
AU Burckhardt, G.; Zimmer, C.; Luck, G.
CS Forschungszent. Molekularbiol. Med., DAW, Jena, E. Ger.
SO Nucleic Acids Res. (1976), 3(3), 537-59
CODEN: NARHAD
DT Journal
LA English
AB Differences in the interaction of poly-L-histidine with **DNA** of various base compn. were demonstrated using melting and CD measurements. The 2 types of **complexes** formed with **DNA** at pH values below pK 5.9 and in the region of pH 6.5 were very different in their CD spectral properties. The binding effects with highly protonated poly-L-histidine were AT-dependent as reflected by large negative CD spectra, indicating the formation of .psi. **DNA** as a condensed state of the double helix. GC-rich **DNA** may, however, also form .psi. **DNA** structures with poly-L-histidine under certain conditions. At pH 6.5, **complex** formation with weakly protonated polypeptide was GC-dependent. Protonated poly-L-histidine apparently interacts more specifically at AT base pairs, probably along the small groove, whereas weakly protonated poly-L-histidine tends to interact preferentially with GC regions which seem to occur in the large groove.
IT **26062-48-6 26854-81-9**
RL: BIOL (Biological study)
(with deoxyribonucleic acids, conformation in relation to)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

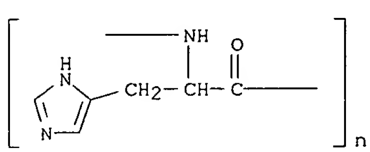
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



```
=> d bib abs l73 15

L73  ANSWER 15 OF 57  USPATFULL
AN     2000:24615  USPATFULL
TI     Polymer composition for delivering substances in living organisms
IN     Summerton, James E., Corvallis, OR, United States
       Weller, Dwight D., Corvallis, OR, United States
PA     AVI BioPharma, Inc., Portland, OR, United States (U.S. corporation)
PI     US 6030941  20000229
AI     US 1997-848844  19970430 (8)
PRAI   US 1996-16347       19960501 (60)
       US 1996-28609       19961023 (60)
DT     Utility
EXNAM  Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala,
       L.
LREP   Gorthey, LeeAnnDehlinger & Associates
CLMN   Number of Claims: 20
ECL    Exemplary Claim: 1
DRWN   35 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 2337
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Polymeric compositions effective for delivering compounds in living
       organisms are described. The compositions include polypeptides which
       exhibit solubility in both hydrophilic and lipophilic environments by
       undergoing a reversible pH-dependent transition from a low-pH,
       lipophilic form to a high-pH, hydrophilic form.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d kwic 15


L73  ANSWER 15 OF 57  USPATFULL
SUMM   Lipid layers, such as comprise cell membranes and the
       extracellular matrix of the stratum corneum, can constitute a formidable
       barrier to drug delivery. For optimal delivery, a.  .  .
SUMM   .  .  .  or related processes. In this process, compounds are taken into
       the cell via progressive invagination of a region of the
     membrane, eventually forming a closed vesicle, or endosome,
       within the cell. In most cases, the endosome then merges with a
       lysosome,.  .  .
DRWD   FIG. 2C shows the complex in its low pH form, which exists in the
       late-stage endosome, entering the lipid membrane, and
       converting back to the high pH form upon contacting the higher pH
       cytosol;
DETD   .  .  .  region of a polypeptide is often effective to initiate entry of
       the polypeptide into a lipid phase, such as a membrane, even
       though regions of the polypeptide more remote from the lipid phase may
       be in a hydrophilic conformation.
DETD   "Endocytosis" is a process by which extracellular material is taken into
       a cell via an invagination of the cell membrane, which closes
       to form a vesicle within the cell known as an endosome. Endocytosis may
       be receptor-mediated, where the extracellular.  .  .  receptor on the
       cell surface, or extracellular compounds may be imported
       nonspecifically, by virtue of their presence near the cell
     membrane. The latter process is also known as fluid-phase
       endocytosis or pinocytosis. A related process, potocytosis, takes
       compounds into the cell.  .  .
DETD   .  .  .  an endosome 14. The pH within the endosome decreases due to the
       action of ATP-driven proton pumps within the endosomal membrane
       (see e.g. Clague, Fuchs). The composition converts, in the increasingly
       acidic environment of the late stage endosome, shown at 16, to its
       low-pH lipid-soluble form, which enters the endosomal membrane
       .
DETD   Upon contacting the cytosolic face of the endosomal membrane,
       the composition is actively drawn into the cytosol by virtue of
       progressive ionization and solvation of the polypeptide chain at.  .  .
```

This unidirectional active transport process is illustrated further in FIGS. 2B and 2C, where only a portion of the endosomal **membrane** is represented.

DETD The above figures depict the polypeptide assuming a completely hydrogen-bonded conformation prior to entering the endosomal **membrane**. Such is likely to occur when the polypeptide is of a composition that readily forms an .alpha.-helix at relatively high. . . pH. However, for highly polar peptides, i.e. those containing a high percentage of acid side chain residues, entry into the **membrane** may be initiated by a localized lipophilic region of the polypeptide, even when other regions of the polypeptide are in. . .

DETD . . . composition of the invention, as can be seen from the above description, is that endosome-to-cytosol transport may be achieved without **disruption** of the endosomal **membrane**, thus avoiding leakage of lysosomal enzymes into the cytosolic compartment of the cell.

DETD B1. Acidic **Amino** Acids. To provide the **free** carboxyl groups which are able to inter-hydrogen bond when the polypeptide is in an .alpha.-helical conformation, carboxyl side chain amino. . .

DETD . . . should not contain moieties which are cationic when the polymer is in its low-pH a-helical conformation (i.e., arginine, lysine, and **histidine**). (An exception is the use of low levels of amino acids such as lysine as sites for attachment of the. . .

DETD With the exception of **nucleic acids**, **polymers** with a high density of acid moieties are not natural components of the interior of cells and so could prove toxic therein. However, such toxicity is much reduced or prevented if, after carrying out its drug transport function, said **polymers** are disassembled into natural subunits endemic in the cytosol of cells. In this regard, it is known that unstructured polypeptides composed of natural L-amino acids can be rapidly depolymerized in the cytosol of cells, primarily in **complex** multi-ring structures called proteasomes.

DETD For delivery of particularly large and/or polar compounds, which do not diffuse across a lipid **membrane** at a practical rate, such delivery is facilitated when the polymer, in its .alpha.-helical conformation, is longer than the thickness of the **membrane**. In this case, at least a portion of the polypeptide is able to enter the cytosol and convert to its. . . a process energetically favored by solvation and ionization, before the large and/or polar compound is required to enter the lipid **membrane**, as illustrated in FIG. 7A.

DETD . . . a polypeptide a-helix, each amino acid residue contributes approximately 1.5 .ANG. to the axial length. Since lipid bilayers of cell **membranes** in eukaryotic cells are typically about 33 to 36 .ANG. thick, a preferred length for the polymer composition is about. . .

DETD . . . lipophilic form is present at an equilibrium concentration sufficient to effect diffusion of the polypeptide into and across the lipid **membrane**. Only for attached compounds which significantly interfere with this diffusion, as described above, is it necessary for the polypeptide to completely span the **membrane** at any given time.

DETD As discussed further below, entry into a cell **membrane** is most likely to be initiated at a terminus of the polypeptide, especially for more polar polypeptides. In longer polypeptides,. . . about 200 amino acids, the termini are at a low concentration and are statistically less likely to contact the cell **membrane**. In addition, longer polypeptides, by virtue of size alone, may not be efficiently engulfed within an endosome, which is typically. . .

DETD . . . precipitate from water, but do not partition into n-pentanol, at about pH 4. Such polymers also fail to cross cell **membranes** in direct-entry experiments, such as described below and Example 10A, at pH's attainable in endosomes of mammalian cells. Further, when. . . uptake of the drug by increasing aqueous solubility, the polyglutamic acid component of the polypeptide-drug conjugate neither entered the endosomal **membrane** nor transported the drug across the **membrane**. Rather, the carrier was degraded within the fused endosome-lysosome, and the released drug then passively diffused across the lysosomal **membrane** into the cytosol.

DETD . . . explained on the premise that relatively polar polypeptides (e.g., containing over about 50% glutamic acid residues) begin entry into cell **membranes** via one or the other termini of the polypeptide, as discussed further below. Because high-glutamic polypeptides with unmodified termini have. . . the C-terminus and the N-terminus, they are apparently unable to efficiently initiate entry into the nonpolar interior of a cell **membrane**.

DETD . . . glutamic acid residues, when modified to provide local lipophilicity at one or both termini, as described in below, crossed cell **membranes** in direct-entry experiments, as described in Example 10A. Such modified high-glutamic polypeptides are also able to partition into n-pentanol from. . .

DETD . . . even when the pH of the aqueous phase is as low as 4. Polyaspartic acid also fails to cross cell **membranes** in direct-entry experiments, such as described in below. Such lack of lipophilicity is expected, both on the basis of partitioning. . .

DETD . . . described above (i.e., leucines at residue positions C2, C3, and C5; see FIG. 8C) afforded quite good transport across cell **membranes**. The polypeptide showed good solubility in n-pentanol, though not in n-octanol, at acidic pH.

DETD . . . the terminus, or a shielding group as described above, may be effective to initiate entry of such polypeptides into a **membrane** .

DETD . . . polypeptide, shown in FIG. 8A, did not partition into n-octanol or n-pentanol, nor did it show any transport across cell **membranes** in direct entry studies.

DETD . . . by initiating the polypeptide synthesis with a .beta.-alanine, as shown in FIG. 10. These modifications afforded modest transport across cell **membranes** (FIG. 8B), and the polypeptide partitioned into n-pentanol, but not into n-octanol.

DETD In operation, once the initiator moiety at the terminus of a polypeptide has entered the **membrane**, succeeding segments of the polypeptide are able to convert to a lipophilic, hydrogen-bonded conformation. Such conversion is driven by the. . . as the increased local lipophilicity provided by the adjacent .alpha.-helical segments of the polypeptide and the proximity of the cell **membrane**.

DETD . . . of the initiator moiety, a polypeptide having a large number of acid side chains is able to partition into the **membrane** in a "stepwise" manner, in which an acid side chain positioned immediately adjacent to the **membrane** forms a hydrogen-bonded pair with a nearby acid side chain, and the segment of the polypeptide containing this pair, having assumed a lipophilic .alpha.-helical conformation, enters the **membrane**.

DETD In this sense, the spacing between carboxylic acid side chains is of particular importance. When a polypeptide enters a **membrane** in the stepwise manner described above, a carboxylate side chain adjacent to the **membrane** which is unable to pair with another carboxylate side chain is likely to block further entry. As noted above, spacings. . .

DETD . . . motive force for unidirectional transport is provided by ionization and hydration of the side-chain carboxyls once the polypeptide spans the **membrane** and encounters the higher-pH cellular cytosol. Thus a polypeptide having a high percentage of side chain carboxyls is expected to provide a high driving force to transport an attached compound across the **membrane**.

DETD . . . of such modifications, or in the absence of a lipid layer. Transport through a thin lipid layer, such as a **membrane**, to an aqueous compartment is also facilitated by ionization and solvation as the composition converts back to a hydrophilic conformation. . .

DETD . . . composition as described herein can function as a molecular engine, pulling the relatively polar compound into and through the endosomal **membrane**. The motive force exerted by the engine is generated as the non-ionic lipophilic .alpha.-helical polypeptide undergoes ionization and solvation at the cytosolic face of the endosomal **membrane**, as illustrated in FIG. 7A. This motive force is, in part, a function of the difference between the transition pH. . . the more power such an engine should exert, and hence the greater the load it can transport through the endosomal **membrane** . For compounds which are fairly small and/or of only moderate polarity, the polymer composition used for endosome-to-cytosol transport may have.

. .

DETD . . . is too low, endosome/lysosome fusion can occur before the polypeptide engine converts to its lipophilic form and enters the encompassing **membrane,** leading to enzymatic degradation of the polypeptide (assuming it comprises L-amino acids) before it can carry out its transport function.. . .

DETD . . . studies. Therefore, partitioning studies are ideally followed by in vitro cell entry experiments, as described below, to further assess the **membrane** transport properties of a composition. A candidate polypeptide may also be tested for binding to serum proteins by performing electrophoresis. . .

DETD . . . the chain. As discussed above, random attachment or high loading of compounds along the chain can impede partitioning into the **membrane,** especially for high acid side chain polypeptides.

DETD . . . pharmaceutical research to estimate the partitioning of that compound between an aqueous compartment and a lipid bilayer of a cell **membrane.** Partitioning between n-octanol and a series of buffers of varying pH was used to provide a quantitative measure of the. . .

DETD B1. Direct Entry. In screening polymer compositions for delivery of a selected compound, direct **transmembrane** passage can be assessed by brief stepwise reduction of the pH of the extracellular medium, which emulates the progressive pH reduction which occurs in an endosome due to the action of proton pumps embedded in its **membrane.** The process is also representative of direct entry in vivo when the pH of the extracellular medium is lower than. . .

DETD After direct-cell-entry studies have demonstrated that one or more polymers are effective for **transmembrane** delivery of a selected compound, cell entry via endocytosis may be assessed by methods such as that described in Example. . .

DETD . . . into the cytosol of eukaryotic cells comprises multiple steps, principal of which are the initial endocytotic uptake and the subsequent **transmembrane** passage from the acidified endosome to the neutral cytosol.

DETD . . . in support of the invention have shown that D- and L-polypeptides having the same sequence exhibit the same partitioning and **membrane** transport properties.

DETD . . . by a plasmid contained in the treated cells. If the antisense oligomer gains access to the cytosolic compartment of the **transfected** cells, a significant reduction in luciferase activity upon dexamethasone induction, relative to untreated cells, should be observed.

DETD . . . likely serve to increase the concentration of the polymer-compound at the cell surface, such that upon invagination of the cell **membrane** to form the endosome, a larger amount of polymer-compound is enveloped therein than would otherwise be the case.

DETD . . . the polymer-compound is released free in the cytosol rather than remaining linked to the lipid anchor embedded in the endosomal **membrane.**

DETD In a further experiment, also described in Example 10, using the polypeptide-antisense oligo composition described above, a tetracationic lipid anchor (**Transfectam**.TM., from Promega Corp., Madison, Wis., USA) was added to enhance the endocytosis step by complexing with the polyanionic polymer composition.. . .

DETD FIG. 12 illustrates the likely role that a lipid anchor such as **Transfectam**.TM. plays in enhancing the initial endocytotic step, followed by its dissociation from the polymer when the polymer converts to its. . .

DETD . . . be specifically exploited, as in treatment of H. pylori infection, by using a polymer composition effective to partition into a **membrane** at a pH less than about 4.5. Other compartments in the body, including the endosomal compartments of eukaryotic cells, which. . .

DETD In order to penetrate a bacterial cell, a composition must be able to cross the outer **membrane** (in gram negative bacteria), the cell wall and the inner plasma **membrane.** The bacterial cell wall generally excludes entry of globular compounds of 2000 Da or more. Studies in support of the. . .

DETD . . . pH environment, may be targeted by an antineoplastic drug linked to a polypeptide which is effective to partition into a **membrane** at the pH present in this extracellular environment.

Such drugs include, for example, cis-platin, antimetabolites such as methotrexate and fluorouracil,. . .

DETD . . . the site of decay or potential decay according to the methods described above, using polypeptides effective to partition into a **membrane** at a pH in the range of about 4.5 to 6.5, and preferably in the range of about 4.5 to. . .

DETD . . . remain at or near the cell surface, going through cycles of opening and closing. Upon closing, proton pumps within the **membrane** produce a pH of about 6.0 within the caveola.

DETD . . . low, the vitamin, with attached polymer, is released from the receptor (Anderson). The polymer-compound composition then inserts into the lipid **membrane,** after undergoing a pH-dependent transition into a lipophilic conformation, and thereafter transports into the cytosol, according to the mechanism described. . .

DETD . . . been reported using folate (Mathias) and epidermal growth factor (Deshpande). D-cycloserine has been reported to facilitate transport through the cytoplasmic **membrane** of bacteria (Chopra, Rapaport).

DETD . . . transported across a cell by transcytosis. In the case of polarized endothelial cells (i.e., cells having distinct apical and basolateral **membranes**) within a capillary, the compound is first taken through the apical **membrane** in the inner capillary wall into a transcytotic vesicle. Such a vesicle typically attains a pH of about 6.0. The vesicle transfers the compound to the basolateral **membrane** of the endothelial cell, on the outer capillary wall. The compound is then expelled from the transcytotic vesicle, thereby releasing. . .

DETD . . . be effected by linking the compound to a polypeptide of the present invention which is effective to partition into a **membrane** at a pH within a selected range, as described below. The composition is preferably further linked to a receptor signal,. . .

DETD . . . the above description, it can be seen that the pH at which the polymer is effective to traverse a cell **membrane** should be between 5.0 and 6.0, or, more generally, below the pH of the transcytotic vesicle in an endothelial cell. . . the pH were above 6.0, in this case, the polymer would assume its lipophilic conformation within the transcytotic vesicle and **penetrate** its **membrane,** thus entering the endothelial cell instead of the targeted brain cell.

DETD . . . and 0.62 g of fluorenylmethoxycarbonyl (FMOC) .beta.-alanine 2 is added, followed by 316 .mu.l of N,N'-diisopropyl carbodiimide and 41 .mu.l N-**methylimidazole**. This slurry is incubated with agitation at 37.degree. C. for 100 minutes, then washed thoroughly with NMP, followed by CH.sub.2. . .

DETD . . . linkage is that it is relatively stable in the extracellular compartment and within endosomes, but after transport across the endosomal **membrane** it is readily cleaved in the cytosolic compartment. The following specific examples illustrate applications of this method.

DETD . . . (1991). The carboxyl group of this species is activated as the N-hydroxysuccinimde ester with N-hydroxysuccinimde using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (Aldrich) and 4-**dimethylaminopyridine** in dichloromethane. The product is dissolved in DMF and treated with 2-aminoethanethiol hydrochloride and triethylamine. The reaction mixture is diluted. . .

DETD . . . Preparation of a thioether-linked polypeptide-cyclosporin conjugate. Cyclosporin A metabolite 17 (see Example 3A) is treated with chloroacetic anhydride in 1:1 dichloromethane/**pyridine** to form an acid chloride (see FIG. 11). The excess reagent is quenched by the addition of water, and the. . .

DETD . . . Example 3A) is treated with the FMOC derivative of glycine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (Aldrich) in dichloromethane in the presence of 4-**dimethylaminopyridine** catalyst. The reaction mixture is washed with acid and base to remove excess reagents and the product chromatographed on silica. . . triethylamine in DMF at 50 degrees C. for one hour. The triethylamine is removed by evaporation under vacuum and the **free amino** derivative mixed with the activated polypeptide above. The solution is evaporated in vacuo to a minimum volume and allowed to. . .

DETD . . . (1991). The carboxyl group of this species is activated as the N-hydroxysuccinimde ester with N-hydroxysuccinimde using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (Aldrich) and 4-**dimethylaminopyridine** in dichloromethane. After washing to remove excess reagents and byproducts, the ester is isolated by evaporation and mixed with the. . .

DETD . . . polypeptide R.sub.1 -NH.sub.2, as defined above, shown at 4, precipitated from aqueous solution as described in Example 2B(iii), having a **free amine** moiety on the N-terminus. DMF (150 .mu.L) is added and the mixture stirred in a warm water bath till dissolution. . .

DETD The above procedure provides information on how low the pH must be in order to effect **transmembrane** transport of a given polypeptide composition of the invention, including, when desired, the attached compound to be transported.

DETD 1.) Without Endocytosis Enhancer. Hela cells used in this functional assay were stably **transfected** with a plasmid containing a mouse mammary tumor virus promoter (inducible with dexamethasone) controlling a gene coding for the 5'. . . from this gene construct. Accordingly, if the antisense oligomer of FIG. 13 gains access to the cytosolic compartment of these **transfected** cells, it should effect a significant reduction in luciferase activity upon dexamethasone induction, relative to untreated cells. Such a reduction. . .

DETD . . . oligonucleotide product prepared as in Example 6C was suspended in culture medium at a concentration of 5 .mu.M. The above-described **transfected** Hela cells were treated with the suspension for 5 hours, and then treated for 16 hours with dexamethasone to induce. . .

DETD . . . with the following changes: a) the concentration of the polypeptide-Morpholino product in the medium was only 300 nM, and b) **Transfectam** (Promega Corp., Madison, Wis.) was added at a concentration of 20 .mu.g/ml. It was expected that the tetra-cationic **Transfectam** would bind electrostatically to the polyanionic polypeptide (in its high-pH form), and the two long-chain alkane moieties of the **Transfectam** would serve as a lipid anchor to substantially increase the effective concentration of the complexed polypeptide-Morpholino product at the cell. . .

DETD TABLE 4

Treatment	Relative Light Units
medium alone	78
Transfectam	97
Transfectam + polypeptide-Morpholino product	35

DETD The increased inhibition of luciferase activity in the cells treated with the combination of **Transfectam** and polypeptide-Morpholino product again suggests that the polypeptide transported this antisense oligo from the endosome into the cytosol of the. . .

=> d bib abs l73 12

L73 ANSWER 12 OF 57 USPATFULL
AN 2000:87731 USPATFULL
TI Methods and compositions for using **membrane-penetrating** proteins to carry materials across cell **membranes**
IN Draper, Rockford, Plano, TX, United States
PA Board of Regents, The University of Texas Systems, Austin, TX, United States (U.S. corporation)
PI US 6086900 20000711
AI US 1998-47148 19980324 (9)
PRAI US 1997-42056 19970326 (60)
DT Utility
EXNAM Primary Examiner: Guzo, David
LREP Arnold, White & Durkee
CLMN Number of Claims: 62
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 2729
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods and compositions delivery of agents into the cytoplasm of cells. Particularly, it concerns the use of **membrane-penetrating** toxin proteins to deliver drugs to the cytoplasm of target cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 12

L73 ANSWER 12 OF 57 USPATFULL
TI Methods and compositions for using **membrane-penetrating** proteins to carry materials across cell **membranes**
AB . . . present invention provides methods and compositions delivery of agents into the cytoplasm of cells. Particularly, it concerns the use of **membrane-penetrating** toxin proteins to deliver drugs to the cytoplasm of target cells.
SUMM . . . major problem in the practical application of many new therapeutic agents is that the agents do not readily cross cellular **membranes** and thus cannot reach compartments within the cell where their sites of action may reside. There are numerous reasons why agents are unable to **penetrate** cell **membranes** including the intrinsic charge, size, and chemical composition of the agents. Potentially therapeutic molecules such as nucleic acids, oligonucleotides, proteins,. . .
SUMM Prior art methods facilitate the passage of some of these agents across **membranes**, but the methods are usually not highly efficient nor are they readily applied to an intact organism, or both. Moreover,. . . type by specifically binding to features of the desired target cell. For example, the passage of nucleic acids across a **membrane** and into cells can be facilitated by methods such as electroporation, calcium phosphate precipitation, and liposome-mediated **transfection** and attachment to facilitating peptides. These methods often are **membrane disruptive** and damage cells, limiting their effectiveness in vivo, or are not able to specifically deliver to desired target cells.
SUMM . . . therefore, an object of the present invention, to provide compositions and methods for the transfers of various molecules across biological **membranes**. A variety of different uses for these compositions and methods are contemplated, as described further below.
DETD . . . the affected cell where the site of action lies. While a number of different approaches have been attempted, the cellular **membrane** remains, both literally and figuratively, a formidable barrier to success in this area.
DETD In this regard, there are certain proteins that have the advantageous

property of being able to pass through **membranes** into cells. Moreover, the proteins bind to receptors as a prerequisite for passing through a **membrane** which offers the opportunity to target only cells that have the receptors. These proteins, which will be termed hereafter as **membrane-penetrating** proteins (MPPs), include, but are not limited to, several plant and bacterial protein toxins, such as ricin, abrin, modeccin, diphtheria. . .

DETD . . . an improved understanding of the molecular basis for toxicity, however, it is possible that the advantageous aspects of toxins (i.e., **membrane penetration**) can be retained while eliminating the undesirable toxicity. With ETA, for example, there is information on the regions of the. . .

DETD The present invention employs a group of proteins known as **membrane penetrating** proteins, of which ETA is an example, to carry a variety therapeutic agents across the cellular **membrane** and into the cytoplasm. There are multiple advantages to such a technique, including decreased doses of therapeutic agents, effective targeting. . .

DETD . . . site to which a therapeutic agent of choice may be attached to facilitate the transport of the agent across a **membrane** into the cell cytoplasm. An "agent" as defined herein is any molecule that is to be transported across a **membrane** by the ETA compositions of the present invention. Examples of the agent of choice include but are not limited to. . .

DETD . . . or methylated DNA or RNA, may be attached to an MPP to facilitate the passage of the agent across a **membrane**. Examples include, but are not limited to, DNA encoding genes; antisense oligonucleotides of any kind; RNA molecules that have been. . . has therapeutic potential if the effectiveness of the drug could be enhanced by facilitating passage of the drug through a **membrane** and into a target cell. Examples include, but are not limited to, drugs that may have anti-tumor activity; drugs that. . .

DETD . . . of compounds to an MPP so that they can be therapeutically transferred into cell cytoplasm. It is contemplated that any **membrane penetrating** protein may be employed in the present invention. As detailed here, ETA has been employed as an exemplary MPP of. . .

DETD . . . form of ETA has been subdivided into three domains, the receptor binding domain (domain I, residues 1-252 and 365-404), the **membrane penetrating** domain (domain II, residues 253-364), and the enzymatic ADP-ribosylation domain (Domain III, residues 405-613). The domains of ETA have been. . .

DETD . . . first step is binding to a cell surface receptor followed by endocytosis of the toxin. The second step is the **penetration** of the toxin through a **membrane** and into the cell cytosol. The third step is the inactivation of protein synthesis by the toxin that has passed through a **membrane**, which kills the cell. Events occurring in these steps is described in more detail in the following paragraphs.

DETD . . . though ETA is in vesicles in the cell at this point, it is still separated from the cytoplasm by a **membrane** barrier, just as if it were still outside the cell. This caveat applies to any material that has been endocytosed: the material still must **penetrate** a **membrane** to reach the cytoplasm.

DETD The second step in the mechanism ETA of action, **penetration** through a **membrane**, is not well-understood, but there are nevertheless several important facts known about the process. One fact is that ETA must be proteolytically cleaved before passing through a **membrane** (Ogata et al., 1990, 1992). Cleavage is between Arg279 and Gly280 of domain II, creating an N-terminal polypeptide of about. . . domain II and all of domain III and is the part of ETA that is known to pass through a **membrane** and enter the cytoplasm. Cleavage is effected by the protease furin, a subtilisin-like protease (Gordon and Leppla, 1994). Once cleavage. . .

DETD . . . have further provided clues to events that occur during part of the process by which the toxin passes through a **membrane**. Drugs that elevate the pH within the vacuolar compartment inhibit the entry of ETA into the cytosol, suggesting that the toxin needs to be exposed to a low pH before passing through a **membrane**. Exposure to a low pH may be needed to cause a conformational change in

the toxin that is important for some later step of entry. The identity of the intracellular compartment through whose **membrane** the toxin actually passes to reach the cytoplasm is not clear. It is known, however, that four of the last. . . NO:12) receptor and that ETA may reach the interior of the ER before penetrating to the cytosol through the ER **membrane** (Pastan et al., 1992; Pelham et al., 1992). In support of the idea that ETA enters the ER en route. . .

DETD . . . (Lukac et al., 1988). It is this modified form which can be used as the vehicle to carry material across **membranes** so that there is no harm to the cell by ETA itself.

DETD The present invention may be used to transport a variety of compounds across a **membrane** and into the cell cytoplasm by using an MPP carrier. In a particular example of such transport, PNAs are transported. . . the present invention to transport any peptide or other molecule, that lends itself to conjugation with an MPP, across the **membrane** and into the cytoplasm where such a molecule may exert its effect.

DETD . . . feature that this cysteine is in the 37 kDa furin fragment of ETA that is known to pass through a **membrane** and enter the cytoplasm. Thus although in preferred embodiments the cysteine residue is inserted at position 612 it is contemplated. . .

DETD . . . that the essence taught by this invention is that an agent attached to an MPP will be carried across a **membrane,** and that there are many ways one skilled in the art may attach agents to an MPP, including but not. . .

DETD The enzymatic, cytotoxic and **membrane penetrating** activities of ETA and any modified ETA may be measured using assays well known to those of skill in the. . .

DETD . . . transport of the molecule may be tested by fractionating the cell to determine whether the labeled fraction is in the **membrane** fraction or in the soluble fraction. If the label appears in the soluble fraction it will be indicative of the. . .

DETD . . . in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or **histidine** ; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; **histidine** to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine. . .

DETD . . . UGU

Aspartic acid	Asp	D	GAC GAU
Glutamic acid	Glu	E	GAA GAG
Phenylalanine	Phe	F	UUC UUU
Glycine	Gly	G	GGA GGC GGG GGU
Histidine	His	H	CAC CAU
Isoleucine	Ile	I	AUA AUC AUU
Lysine	Lys	K	AAA AAG
Leucine	Leu	L	UUA UUG CUA CUC CUG. . .

DETD . . . phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); **histidine** (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

DETD . . . lysine (+3.0); aspartate (+3.0.+-.1); glutamate (+3.0.+-.1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5.+-.1); alanine (-0.5); **histidine** (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4).

DETD By employing a promoter with well-known properties, the level and pattern of expression of a polynucleotide following **transfection** can be optimized. For example, selection of a promoter which is active in specific cells, such as tyrosinase (melanoma), alpha-fetoprotein. . .

DETD . . . expression system is another possible embodiment. Eukaryotic cells can support cytoplasmic transcription from certain bacteriophage promoters if the appropriate bacteriophage **polymerase** is

provided, either as part of the delivery **complex** or as an additional genetic expression **vector**.

DETD . . . in vivo by including a marker in the expression vector. The marker would result in an identifiable change to the **transfected** cell permitting easy identification of expression. Usually the inclusion of a drug selection marker aids in cloning and in the. . .

DETD . . . subunit, E. coli enterotoxin toxin A subunit, cholera toxin A subunit and pseudomonas toxin c-terminal. Recently, it was demonstrated that **transfection** of a plasmid containing the fusion protein regulatable diphtheria toxin A chain was cytotoxic for cancer cells. Thus, transfer of. . .

DETD . . . (Demidov et al., 1994). These properties make PNAs extremely attractive as antisense therapeutic agents; however, PNAs do not readily cross **membrane** barriers, which prevents them from reaching intracellular sites of action unaided (Wittung et al., 1995). Therefore, a PNA is attached. . .

DETD . . . include derivatives of natural compounds like carbohydrates, amino acids or nucleic acids that react with cellular enzymes but which cross **membranes** poorly. Totally synthetic drugs that cross **membranes** poorly would also be candidates.

DETD . . . about 1:1, respectively, in the presence of an agent or agents (chemical or electrical) that promote the fusion of cell **membranes**. Fusion methods using Sendai virus have been described (Kohler and Milstein, 1975; 1976), and those using polyethylene glycol (PEG), such. . .

DETD . . . an agent that blocks the de novo synthesis of nucleotides in the tissue culture media. Exemplary and preferred agents are **aminopterin**, methotrexate, and azaserine. **Aminopterin** and methotrexate block de novo synthesis of both purines and pyrimidines, whereas azaserine blocks only purine synthesis. Where **aminopterin** or methotrexate is used, the media is supplemented with hypoxanthine and thymidine as a source of nucleotides (HAT medium). Where. . .

DETD . . . the second peak was unreacted ETA. This order of elution is consistent with the fact that the PNA has a **free amino** group at the N-terminus that is protonated at neutral pH so that the conjugate containing the PNA is eluted from. . .

DETD . . . into a composition in a neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts (formed with the **free amino** groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or. . . inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, **histidine**, procaine and the like.

DETD . . . If so, it would indicate that the attached PNA did not block the ability of ETA to pass through a **membrane**, inferring that the PNA also was carried through the **membrane** with the ETA.

DETD To evaluate the ability of ETA-.OMEGA.Cys612-PNA to **penetrate** a **membrane** and reach the cytoplasm, the inventor incubated serial dilutions of the conjugate with mouse LMTK.sup.- cells which are extremely sensitive. . . the cytoplasm despite the presence of the attached PNA. This is evidence that ETA can carry a PNA across a **membrane** and into the cytoplasm.

DETD . . . small increase in the IC.sub.50 considering that the toxin must now drag a PNA with it when it crosses a **membrane**. Note also that there was no change in the IC.sub.50 when two-times purified material was used. This indicates that the. . . this data teaches that attaching a PNA to ETA-.OMEGA.Cys612 slightly reduces the efficiency at which the toxin can cross a **membrane**, but that it nevertheless does cross and presumably carries with it the PNA.

DETD Guo et al., "**Disruptions** in Golgi structure and **membrane** traffic in a conditional lethal mammalian cell mutant are corrected by .sub.-- -COP." J. Cell Biol., 125:1213-1224, 1994.

DETD . . . "Isolation of three classes of conditional lethal Chinese hamster ovary cell mutants with temperature-dependent defects in low density lipoprotein receptor **stability** and intracellular **membrane** transport," J. Biol. Chem., 269:20958-20970, 1994.

DETD Lin and Guidotti, "Cloning and expression of a cDNA coding for a rat liver plasma **membrane** ecto-ATPase: the primary structure of

the ecto-ATPase is similar to that of human biliary glycoprotein," J. Biol. Chem., 264:14408-14414, 1989.

DETD Tatu et al., "**Membrane** glycoprotein folding, oligomerization and intracellular transport: effects of dithiothreitol in living cells," EMBO J., 12:2151-2157, 1993.

DETD Wittung et al., "Phospholipid **membrane** permeability of peptide nucleic acid," FEBS Letters, 365:27-29, 1995.

DETD Zhao and London, "Conformation and model **membrane** interactions of diphtheria toxin fragment A," J. Biol. Chem., 263(30):15369-15377, 1988.

=> d bib abs l73 18

L73 ANSWER 18 OF 57 USPATFULL
AN 1999:137233 USPATFULL
TI Self-assembling polynucleotide delivery method
IN Szoka, Jr., Francis C., San Francisco, CA, United States
Haensler, Jean, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States (U.S. corporation)
PI US 5977084 19991102
AI US 1995-480446 19950607 (8)
RLI Division of Ser. No. US 1992-913669, filed on 14 Jul 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-864876, filed on 3 Apr 1992, now abandoned
DT Utility
EXNAM Primary Examiner: Marschel, Ardin H.
LREP Koenig, Nathan P.Crosby, Heafey, Roach & May
CLMN Number of Claims: 49
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 1784
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a self-assembling polynucleotide delivery system comprising components aiding in the delivery of the polynucleotide to the desired address which are associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and **membrane**-permeabilization components, and subcellular localization components. Specific compounds useful in this system are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 18

L73 ANSWER 18 OF 57 USPATFULL
AB . . . associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and **membrane**-permeabilization components, and subcellular localization components. Specific compounds useful in this system are also provided.
SUMM . . . associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and **membrane**-permeabilization components, and subcellular localization components.
SUMM . . . & Dorner, 1991). The locus of the disease has been traced to mutations in the gene encoding the cystic fibrosis **transmembrane** conductance regulator (CFTR). J. R. Riordan et al., Science (1989) 245:1066-1073; B. Kerem et al., Science (1989) 245:1073-1080. Correction of. . .
SUMM . . . CFTR to the cotton rat lung in vivo. M. A. Rosenfeld et al., Cell (1992) 68:143-155. Although high levels of **transfection** in vivo have been reported with the adenoviral vectors, non-viral delivery systems have a number of advantages and should be. . .
SUMM . . . These techniques are applicable to gene therapy if the target cells can be removed from the body, treated, and the **transfected** cells amplified and then returned to the patient. This option is not possible for CF patients. At present the best in vivo **transfection** efficiencies are obtained with retroviruses (Bluestone, supra) and adenoviruses (Rosenfeld et al., supra). However the efficiency is variable and a. . .
SUMM . . . phosphate or a cationic facilitator (Felgner et al., supra). Other popular methods involve DNA injection during physical puncture of the **membrane** (M. R. Capecchi, Cell (1980) 22:479-485) or

passive uptake during permeabilization or abrasion of the cellular **membrane** (Felgner et al., supra). Each method is intrinsically aggressive and applicable only in vitro.

SUMM . . . is not necessary to encapsulate the DNA inside of the liposome with the cationic reagents. Lipofectin.TM. has been used to **transfect** reporter genes into human lung epithelial cells in culture (L. Lu et al., Pfluaers Arch (1989) 4:198-203), to introduce the. . . supra) but the level of expression was not quantitated. When chloramphenicol acetyltransferase (CAT) attached to a steroid sensitive promoter was **transfected** into rat lung, expression could be positively regulated by dexamethasone. Hazinski et al., supra. Cytotoxicity is a problem with high. . .

SUMM . . . Res Comm (1991) 179:280-285). These have been used to mediate gene transfer in culture. Although there is some improvement over **transfection** rates observed with Lipofectin.TM. (about threefold), toxicity remains a problem. Studies on the mechanism responsible for **transfection** using the cationic lipids have been notably lacking. The past approach has been to synthesize different cationic lipids and try them in **transfection** assays, rather than to systematically study how the delivery systems introduce DNA into the cell. DOTMA/PE liposomes can undergo bilayer. . . anionic liposomes (N. Duzgunes et al., Biochem (1989) 28:9179-9184) which suggests that direct entry of the DNA via the plasma **membrane** is involved with DOTMA's mode of action. High efficiency **transfection** using cationic lipids systems requires the inclusion of PE, possibly because PE can form **intramembrane** lipid intermediates which facilitate **membrane** fusion. The role of PE in **membrane** permeabilization and fusion has been extensively studied. E.g., M.-Z. Lai et al., Biochem (1985) 24:1646-1653; H. Ellens et al., Biochem. . . .

SUMM Cellular Targeting. Efficient gene transfer requires targeting of the **DNA** to the cell of choice. Recently, procedures based upon receptor mediated endocytosis have been described for gene transfer. G. Y.. . . Wu et al., J Biol Chem (1987) 262:4429; G. Y. Wu et al., J Biol Chem (1988) 263:14621-14624. A cell-specific ligand-**polylysine complex** is bound to **nucleic acids** through charge interactions. The resulting **complex** is taken up by the target cells. Wu et al., supra, reported efficient **transfection** of the human hepatoma cell line HepG2 and of rat hepatocytes in vivo using this delivery system with asialoorosomucoid as. . . targeting. Finally Wagner et al., Proc Natl Acad Sci (USA) (1990) 87:3410-3414 and (1991) 88:4255-4259 observed transferrin-polycation-mediated delivery of a **plasmid** into the human leukemic cell line K-562 and subsequent expression of the encoded luciferase gene. However, the described delivery systems are based upon high molecular weight targeting proteins linked to **DNA** through a **polylysine** linker. These large ligand-polycation **conjugates** are heterogenous in size and composition, not chemically well-defined, and difficult to prepare in a reproducible fashion (Wu et al.,. . . in many of the receptor mediated systems, chloroquine or other disruptors of intracellular trafficking are required for high levels of **transfection**. In one study, adenovirus has been used to enhance gene delivery of the receptor mediated systems. D. T. Curiel et. . .

SUMM Charge Neutralization and **Membrane** Permeabilization. Direct delivery of genes is aided by the ability to neutralize the large negative charge on the polynucleotide, and the (often concomitant) ability to permeabilize the **membrane** of the targeted cell. The use of polycations to neutralize the polynucleotide charge and aid in the **membrane** permeabilization and translocation is well known. Felgner, supra. Cationic lipids have also been used for this purpose. P. L. Felgner. . .

SUMM Y. Kaneda et al., Science (1989) 243:375-378, showed that the **transfection** efficiency obtained with reconstituted viral envelopes is increased when the foreign gene is co-delivered into the target cells with nuclear proteins. DNA mixed with nuclear proteins exhibit a modest increase in **transfection** over DNA that was mixed with albumin (Kaneda et al.). The assumption is that the DNA is incorporated into the. . . al., J Cell Sci Supp (1989) 11:225-242; Silver, supra). The suggestion that nuclear entry is rate limiting for

successful, stable **transfection** is also supported by the finding that plasmid DNA microinjected into the cytoplasm is unable to bring about **transfection** of cells (no **transfection** out of 1000 cytoplasmic injections, whereas microinjection of plasmids directly into the nucleus results in **transfection** in greater than 50% of the microinjected cells. Cappechi, supra. If the attachment of nuclear localization signals on the plasmid leads to transport of plasmid DNA into the nucleus, the **transfection** efficiency should increase. We propose a novel method to attach NLS and other ligands to the desired polynucleotide.

SUMM Finally, investigators have demonstrated that **transfection** efficiencies increase when DNA is condensed using various cationic proteins. T. I. Tikchonenko et al., Gene (1988) 63:321-330; M. Bottger et al., Biochim Biophys Acta (1988) 950:221-228; Wagner et al., supra. The reason why DNA condensation increases **transfection** is not readily apparent, it may increase cellular uptake of DNA (Wagner et al., supra) but it also can decrease. . . .

SUMM . . . polynucleotide with a combination of one or more of the following functional components: DNA-masking components, cell recognition components, charge-neutralization and **membrane** -permeabilization components, and subcellular localization components.

SUMM . . . of one or more, preferably two or more of the following functional components: DNA-masking components, cell recognition components, charge-neutralization and **membrane** -permeabilization components, and subcellular localization components. Each component in this system is able to perform its indicated function and also be. . . .

SUMM . . . a composition for presenting a polynucleotide to a subcellular component of a eukaryotic cell comprising the polynucleotide associated with a **membrane**-permeabilizing component capable of transporting the polynucleotide across the cytoplasmic **membrane** of the eukaryotic cell.

SUMM . . . eukaryotic cell comprising the polynucleotide associated with both a cell recognition component capable of recognizing the eukaryotic cell, and a **membrane**-permeabilizing component capable of transporting the polynucleotide across the cytoplasmic **membrane** of the eukaryotic cell.

SUMM . . . subcellular component of a eukaryotic cell comprising the polynucleotide, a cell recognition component capable of recognizing said eukaryotic cell, a **membrane**-permeabilizing component capable of transporting the polynucleotide across the cytoplasmic **membrane** of said eukaryotic cell, a subcellular-localization component capable of delivering the polynucleotide from the cytoplasm of said eukaryotic cell to. . . .

SUMM . . . group, and Y is selected from the group consisting of masking compound, cell surface receptor ligands, subcellular localization sequences, and **membrane** permeabilizing components.

DRWD . . . one embodiment of the polynucleotide delivery system of the invention, where NLS is a nuclear localization sequence, MD is a **membrane**-permeabilization component, and Ligand is a cell recognition component.

DRWD FIG. 3 compares the efficiency of luciferase **transfection** with Lipofectin.TM., pH-sensitive liposomes, and the gramicidin S/DOPE/DNA complex.

DRWD FIG. 4 shows the effect of gramicidin S to DNA ratio on **transfection** efficiency.

DRWD FIG. 5 shows the effect of gramicidin S to DOPE ratio on **transfection** efficiency.

DRWD FIG. 6 shows the effect of lipid type in the gramicidin S/lipid/DNA complex on **transfection** efficiency.

DRWD FIG. 7 shows the effect of substituting other peptides for gramicidin S in the gramicidin S/lipid/DNA complex on **transfection** efficiency.

DETD . . . art. Some of these substitute linkages are non-polar and contribute to the desired ability of the polynucleotide to diffuse across **membranes**. Others contribute to the increased or decreased biodegradability of the polynucleotide. (Biodegradability will be affected, for example, by increased or. . . .

DETD The term "functional component" as used herein, includes DNA-masking components, cell recognition components, charge-neutralization and

membrane-permeabilization components, and subcellular-localization components.

DETD The term "**membrane**-permeabilizing component", as used herein, refers to any component that aids in the passage of a polynucleotide across a **membrane**. Thus, this term encompasses in part charge-neutralizing components, usually polycations, that neutralize the large negative charge on polynucleotides, and enable the polynucleotide to transverse the hydrophobic interior of a **membrane**. Many charge-neutralizing components can act as **membrane** -permeabilizers. **Membrane**-permeabilization may also arise from amphipathic molecules.

DETD A **membrane** permeabilizer is a molecule that can assist a normally impermeable molecule to traverse cellular **membranes** and gain entrance to the cytoplasm of the cell. A **membrane** permeabilizer may be a peptide, bile salt, glycolipid, carbohydrate, phospholipid or detergent molecule. **Membrane** permeabilizers often have amphipathic properties such that one portion is hydrophobic and another is hydrophilic, permitting them to interact with **membranes**.

DETD . . . with one or more, preferably two or more of the following functional components: DNA-masking components, cell recognition components, charge-neutralization and **membrane** -permeabilization components, and subcellular localization components. Each element in this system is able to perform its indicated function and also be. . .

DETD **Membrane-**Permeabilizing Components. The **membrane** -permeabilizing element of this system is a molecule that aids in the passage of a polynucleotide across a **membrane**. The liposomes and synthetic cationic lipids described above as DNA-masking components also may function as **membrane-**permeabilization components.

DETD The **membrane-**permeabilizing components of this invention also include polycations that neutralize the large negative charge on polynucleotides. Polycations of this invention include. . .

DETD In a different embodiment, the **membrane-**permeabilizing component of the invention is an amphipathic cationic peptide. Amphipathic cationic peptides are peptides whose native configuration is such that. . .

DETD In a particularly preferred embodiment, the **membrane** -permeabilizing element includes, in addition to the amphipathic cationic cyclic peptides, either (1) a lipid, or (2) a simple polyamine, or. . .

DETD The **membrane** permeabilizing elements--the cyclic peptide and optional phospholipid and polyamine--may be added to the composition simultaneously or consecutively. Preferably, the cyclic. . .

DETD . . . moiety will be covalently attached to a functional moiety, said moiety being a cell recognition moiety, subcellular localization moiety, or **membrane** permeabilizing moiety as described above. The value of p determines the separation of the intercalator from the functional moiety. Preferred. . .

DETD Gramicidin S **Transfection**

DETD . . . phosphatidylethanolamine to form a charge complex with the negatively charged DNA. This complex is thought to fuse with the cell **membrane** and deliver DNA into the cytoplasm. An alternative approach uses pH sensitive liposomes composed of a negatively charged lipid and. . . 28:9508-9514. The delivery mechanism involves endocytosis of the liposome, as the pH in the endosome becomes acidic, the liposomal bilayer **destabilizes** and fuses with the endosomal **membrane**. The contents of the liposome are then introduced into the cytoplasm of the cell. C.-J. Chu et al., Pharmaceut Res. . .

DETD Cell **Transfection** Protocol

DETD . . . liposomes, Lipofectin.TM., or the gramicidin S/DOPE/DNA complex, cells were washed once with 2 ml of FCS-free DME H-21 medium. The **transfection** system was then added in 2 ml of the same media. In some experiments, **transfection** took place in 10 FCS containing DME H-21. After 5 hrs. media was removed and replaced by 3 ml of. . .

DETD In order to compare the potency of three different viral luciferase gene promoters, RSV, SV40 and CMV, we have **transfected** several mammalian cell lines with the corresponding Lipofectin.TM.

complexed-plasmids. Each dish of cells received 2 .mu.l of plasmid combined with. . .

DETD Typical **complex** preparation was made by diluting 20 .mu.g of **plasmid DNA** in 300 .mu.l of 30 mM Tris Cl pH 9 in a polystyrene tube. Gramicidin S was diluted in 30. . . solution at 20 mg/ml in DMSO. 20 .mu.l of diluted gramicidin S (i.e. 40 .mu.g) solution was added to the **DNA** and quickly mixed. Then 170 nmoles of liposomes were added slowly drop by drop to the **DNA** / gramicidin S mixture. Liposomes were prepared by drying 4 .mu.moles of lipids under nitrogen with a rotavapor and by. . . 9 Tris Cl buffer. Liposomes were subsequently sonicated 30 min under argon using a bath sonicator. The diameter of the **complex** was determined by dynamic light scattering. Other peptides, including tyrocidine (U.S. Biochemicals), polymyxin B (Sigma) and **polylysine** 100 (Sigma) and the polycationic Starburst.TM. dendrimer (Polyscience, Inc.), were also used to form the **complex** with **DNA** and lipids.

DETD The efficiency of **transfection** was monitored by measuring the expression of luciferase in CV-1 cells as described above. The dose response comparing the amount of DNA added in the three **transfection** systems is illustrated in FIG. 3. Light units per mg cell protein in a log scale are plotted on the. . .

DETD The data presented in Example 2 show that gene expression due to the gramicidin S-DOPE-**DNA complex** is maximal when the negative charges on **DNA** are neutralized by the positive charges on gramicidin. To determine whether charge neutralization or **membrane** permeabilization is more important for gene transfer using this system, the positive charge contribution from gramicidin S was incrementally replaced by the positively charged **polyamine** , spermidine. The gramicidin S-lipid-**DNA complex** was prepared as described in Example 1 except the amount of gramicidin S added to the **complex** was varied at constant amounts of **DNA** (20 ug). The requisite positive charges required to neutralize the **DNA** was supplied by spermidine. The **complex** was prepared with or without 170 nmoles of DOPE. The **complex** was added to CV-1 cells and the luciferase activity measured as described in Example 1. The results are given in. . . luciferase activity expressed as light units/mg cell protein. The first activity was always greater when DOPE was present in the **complex** . In the absence of DOPE, the sequential replacement of positive charge due to gramicidin S by spermidine leads to a. . . response obtained in the presence of DOPE. When the percent of charge neutralization due to gramicidin S dropped below 25% **transfection** activity was totally lost. Thus, **membrane** permeabilization function of gramicidin S is more important than the charge neutralization function.

DETD The peptide-DOPE-**DNA complex** was prepared as described in Example 1 except the type of peptide added to the **complex** was varied at constant amounts of **DNA** (20 ug) and DOPE (170 nmoles). The peptides employed were polymyxin B, a cyclic cationic peptide; **polylysine,** a linear cationic peptide; tyrocidine, a cyclic cationic peptide with a similar structure to gramicidin S but containing only a single positive charge and gramicidin S. The luciferase **plasmid** was also **transfected** into the cells using Lipofectin.TM.. The **complex** was added to CV-1 cells and the luciferase activity measured as described in Example 1. FIG. 7 shows that gramicidin. . . of expression followed closely by the related cyclic peptide tyrocidine. Both cyclic peptides were superior to Lipofectin.TM. at transferring the **DNA** into cells. Activity was also seen with the other two peptides, polymyxin B and **polylysine,** however, the level of luciferase expression mediated by these two cationic peptides was inferior to that induced by gramicidin S. . .

DETD G. Comparison of **DNA**-Dendrimer **Complex** and **DNA-Polylysine Complex-**Mediated **Transfections**

DETD To find better chemically-defined alternatives to the **polyamine polymers** such as **polylysine,** we have employed the hydrophilic branched polycation macromolecules also know as the Starburst.TM. Dendrimer microparticles, Tomalia et al., supra, to form a **complex** with **DNA** or with **DNA** and the permeabilizing amphipathic peptide GALA/SEQ ID NO. 10. R. Parente et

al., Biochemistry (1990) 29:8720-8728. The **complex** was prepared by diluting 12 .mu.g of pCLuc4 **plasmid** in 660 .mu.l of HBS (20 mM Hepes, 150 mM NaCl, pH 7.4) in a polystyrene tube. **Polylysine** (Sigma Chemical Co.) or Starburst.TM. Dendrimer microparticles of the fifth generation (1 nmole) (Polysciences, Inc.) was dissolved in 340 .mu.l of HBS and added slowly (dropwise) to the **DNA** solution. In these conditions, the positive charges from the epsilon amino groups of the **polylysines** or from the peripheral amines of the dendrimers are in 1.3-fold excess over the negative charges of the **plasmids**. When the peptide GALA/SEQ ID NO. 10 was added, it was added so that the negative charges on GALA/SEQ ID. . . after the last addition at room temperature and then 500 .mu.l of the mixture was added to CV-1 cells. The **transfection** protocol was carried out as described above. In this experiment, the best **transfection** protocol was accomplished with the GALA/SEQ ID NO. 10-dendrimer-**DNA complex**, followed by the dendrimer-**DNA** and then by **polylysine-DNA**. The results are shown in Table 2 below.

DETD TABLE 2

DNA-Dendrimer Mediated **Transfection**

Condition	Luciferase lights (units per mg cell protein)
Dendrimer-GALA-DNA	(9 .+-. 2) .times. 10.sup.5 (n = 2)
Dendrimer-DNA (5 .+-. 2). . .	

DETD . . . unprotected amine. Alternatively, a protected peptide containing two adjacent lysine residues is synthesized by solid phase synthesis. The peptide carries **membrane** permeabilization functions or targeting functions and acridine residues are added to the two .epsilon.-amino groups on the lysines.

DETD . . . with a mixture of CH.sub.3 OH/NEt.sub.3 /H.sub.2 O 5:4:1. The bis-trifluoroacetate salt of the spermidine derivative was converted to the **free amine** by passing a water solution of the salt through a small BIO-RAD AG 1.times.2 (OH.sup.-) column. The fractions positive for. . .

DETD . . . evaporation to about 1 ml and the bis-acridine derivative was isolated by chromatography on a silica gel column, eluted with n-Butanol/**Pyridine**/Acetic acid/Water 6:2:1:2.

DETD **Transfection** Assay Using Nuclear Localization Sequences

DETD Cells were **transfected** with 4 .mu.g of liposome-encapsulated plasmid (100 .mu.l of the liposome solution) for 5 hours at 37.degree. C. and luciferase. . .

DETD If we exclude that the peptide-bis-acridines conjugates do not protect DNA from degradation, the observed **transfection** enhancement must be the result of increased nuclear entry. The 4-5 fold increase of **transfection** agrees with published results (Kaneda et al., supra Science (1989) 243:375-378) using proteins that bind to DNA and enhance DNA. . .

DETD . . . method has been described by D. Larwood and F. Szoka, J Labelled Comp & Radiopharm (1984) 21:603-614. Polyethylene glycol 1900 carbonyl-**imidazole** methyl ether was prepared by taking 530 mg (0.28 mmol) dry PEG 1900 monomethyl ether in 2 ml dry methylene chloride and adding 78 mg (0.46 mmol) **carbonyldiimidazole** and 10 mg (0.11 mmole) **imidazole** (sodium salt). After stirring overnight, 6 ml dry methylene chloride were added and the mixture extracted with 3.75 ml water,. . . quantitative yield. Alternatively, the solvent was removed, and the resulting oil recrystallized from chloroform/diethyl ether at -20.degree. C. The resulting **imidazole** carbamate white crystals were filtered through a chilled funnel, rinsed with a small amount of diethyl ether, and used immediately.

DETD The **imidazole** carbamate (0.1 mM) is added to 0.125 mM of N,N'-bis-(9-acridinyl)-4-aza-1,8-diaminooctane ("bis-acridine spermadine", prepared as described by P. Nielsen, Eur. J.. . .

DETD In a similar fashion the non-blocked PEG (molecular weight 6000), is activated as above to form the bis-**imidazole** carbamate PEG. The bis-**imidazole** carbamate PEG is reacted with a 2.5 fold excess of bis-acridine spermidine to form the bis-acridine

spermidine)-PEG 6000.
DETD . . . (cyclic anhydride)
2. monoacyl lysolecithin + cyclic anhydride
CHCl.sub.3, DMAP, 25.degree. C. 48 hr ------>
Lecithin - COOH
3. Lecithin-COOH + **carbonyldiimidazole**
CHCl.sub.3, 25.degree. C., 2 hr --- >
Lecithin **imidazolide**
4. Lecithin **imidazolide** + amine reactant
CHCl.sub.3, 25.degree. C., 24 hr --->
cationic lecithin

DETD The final reaction of the amine reactant with the lecithin **imidazolide** is undertaken immediately after formation of the lecithin **imidazolide**. The lecithin **imidazolide** (0.1 mM) is added to a solution of the amine (0.7 mM) in chloroform. Suitable amines for this coupling are. . .

CLM What is claimed is:

. . . the functional agent selected from the group consisting of: i) a cell recognition agent that recognizes the eukaryotic cell; ii) **membrane**-permeabilizing agent that transports the desired polynucleotide across the cytoplasmic **membrane** of the eukaryotic cell; iii) a subcellular-localization agent that delivers the desired polynucleotide from the cytoplasm of the eukaryotic cell. . .

. . . phenylglyoxal, or ZY, wherein Y is selected from the group consisting of cell surface receptor ligands, nuclear localization sequences, and **membrane** permeabilizing components; n and m are independently an integer of 1 to 20; p is an integer of 0 to. . .

29. The method of claim 1 wherein the functional agent comprises a **membrane**-permeabilization agent.

30. The method of claim 29 herein the **membrane**-permeabilizing agent is selected from the group consisting of polylysine, polyarginine, poly (lysine-arginine), polyamines, dendrimer polycations, cationic bile salts and amphipathic. . .

=> d bib abs l73 24

L73 ANSWER 24 OF 57 USPATFULL
AN 1998:139037 USPATFULL
TI Amines and methods of making and using the same
IN Manoharan, Muthiah, Carlsbad, CA, United States
Cook, P. Dan, Carlsbad, CA, United States
PA ISIS Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)
PI US 5834607 19981110
AI US 1994-361858 19941222 (8)
RLI Continuation of Ser. No. US 1992-943516, filed on 11 Sep 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-558663, filed on 27 Jul 1990, now patented, Pat. No. US 5138045 And a continuation-in-part of Ser. No. US 1992-844845, filed on 3 Mar 1992, now patented, Pat. No. US 5218105
DT Utility
EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Marschel, Ardin H.
LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1649
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel amine compounds are provided by the present invention. Methods of preparing and using said novel amine compounds are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L73 ANSWER 24 OF 57 USPATFULL
SUMM . . . of these agents at specific intracellular targets. One important factor is the ability of antisense compounds to traverse the plasma **membrane** of specific cells involved in the disease process.
SUMM Cellular **membranes** consist of lipid protein bilayers that are freely permeable to small, nonionic, lipophilic compounds and inherently impermeable to most natural. . . . of natural and modified oligonucleotides in cultured mammalian cells have been well documented, so it appears that these agents can **penetrate membranes** to reach their intracellular targets. Uptake of antisense compounds into a variety of mammalian cells, including HL-60, Syrian Hamster fibroblast,. . .
SUMM The **conjugation** of **polyamines** to **oligonucleotides** have been found to enhance cellular uptake of **oligonucleotides**, increased lipophilicity, cause greater cellular retention and increased distribution of the compound. Vasseur, et al., Nucleosides and Nucleotides, 1991, 10,. . . et al. also refers to unpublished results in which the functionalities spermidine and proflavin were employed. Le Doan, et al., **Nucleic Acids** Research 1987, 15, 8643 teaches oligothymidylates covalently linked to porphyrins at their 3' end via one of the linkers --O----CH.sub.2. . . . teaches morpholino subunits, linked together by uncharged, achiral linkages such as amides. As described in PCT/US91/04086 filed Jun. 10, 1991, **polyamines** have also been linked at the 5' end of an **oligonucleotide** at the 5' site of the sugar moiety of the terminal nucleoside and at the 2-position carbon of the heterocyclic. . .
SUMM . . . Formula II may also be prepared enzymatically by providing a starting material having the structure: ##STR4## wherein R.sub.4 is an **oligonucleotide**, R.sub.12 is an **oligonucleotide** and B is urea or a heterocyclic base having a corresponding glycosylase and reacting the starting material with an endonuclease to generate a **conjugated** .alpha.,.beta.-unsaturated system in the sugar

residue of the 3' terminal nucleotide. Thereafter the compound having a **conjugated** .alpha.,.beta.-unsaturated system is reacted with a pendent group containing a nucleophile functionality thereon. Following addition of the pendent group the double bond of the .alpha.,.beta. system is reduced with a reducing agent. A **polyamine** species may then be attached to the pendent group via an alkylation reaction. Alternatively, a **polyamine** species may be attached to a pendent group which is a bifunctional linker.

DETD **Oligonucleotides** may also include species which include at least some modified base forms. Thus, purines and pyrimidines other than those normally. . . ; ONO.sub.2 ; NO.sub.2 ; N.sub.3 ; NH.sub.2 ; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a **conjugate**; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an **oligonucleotide**; or a group for improving the pharmacodynamic properties of an **oligonucleotide** and other substituents having similar properties. Sugar mimetics such as cyclobutyls may also be used in place of the pentofuranosyl. . . entitled Compositions And Methods For Detecting And Modulating RNA Activity; Ser. No. 566,977, filed Aug. 13, 1990, entitled Sugar Modified **Oligonucleotides** That Detect And Modulate Gene Expression; Ser. No. 558,663, filed Jul. 27, 1990, entitled Novel **Polyamine Conjugated Oligonucleotides**; Ser. No. 558,806, filed Jul. 27, 1991, entitled Nuclease Resistant Pyrimidine Modified **Oligonucleotides** That Detect And Modulate Gene Expression; and Ser. No. PCT/US91/00243, filed Jan. 11, 1991, entitled Compositions and Methods For Detecting And Modulating RNA Activity; Ser. No. 777,670, filed Oct. 15, 1991, entitled **Oligonucleotides** Having Chiral Phosphorus Linkages; Ser. No. 814,961, filed Dec. 24, 1991, entitled Gapped 2' Modified Phosphorothioate **Oligonucleotides**; Ser. No. 808,201, filed Dec. 13, 1991, entitled Cyclobutyl **Oligonucleotide** Analogs; and Ser. No. 782,374, filed 782,374, entitled Derivatized **Oligonucleotides** Having Improved Uptake & Other Properties, all assigned to the assignee of this invention. The disclosures of all of the above noted patent applications are incorporated herein by reference. **Oligonucleotides** may also comprise other modifications consistent with the spirit of this invention. Such **oligonucleotides** are best described as being functionally interchangeable with yet structurally distinct from natural **oligonucleotides**. All such **oligonucleotides** are comprehended by this invention so long as they effectively function as subunits in the **oligonucleotide**. Thus, purine containing **oligonucleotide** are **oligonucleotides** comprising at least one purine base or analog thereof. In other embodiments of the present invention compounds of the present. . . may be "subunits" of a species comprising two or more compounds of the present invention which together form a single **oligonucleotide**.

DETD . . . oxidizing agent to produce an dialdehyde-terminated activated oligonucleotide. Suitable oxidants include periodate solution, lead tetraacetate, activated MnO.sub.2, thallium (III) salts, **pyridinium** chlorochromate and O.sub.2 catalyzed by Co (III) salts.

DETD . . . the compound containing the polyamine species with an activated ester having the structure: ##STR13## to form a compound with repeating **imidazole** catalytic cleaver units useful as an antisense therapeutic agents. Heterobifunctional linkers also can be utilized for attachment of intercalators, RNA cleaving agents including **imidazoles**, cell receptor binding molecules, steroids, alkylating agents, crown amines, porphyrins and cross-linkers to the polyamine species.

DETD 1-O-(ortho-nitrobenzyl)-2,3,5-tri-O-benzoyl-D-ribofuranose is deprotected at 2,3,5 positions using ammonia. Tritylation with excess trityl chloride/**pyridine/4-dimethylaminopyridine** gives 3-5-ditrityl-1-O-nitrobenzyl-D-ribo furanose. Oxidation at 2 position with CrO.sub.3 followed by NaBH.sub.4 reduction inverts the configuration at 2 position yielding. . .

DETD The crude 3'-aminolinker-**oligonucleotide** (SEQ ID NO:9) (15 O.D. units, approximately 85 nmols) was dissolved in freshly prepared NaHCO.sub.3 buffer (150 ul, 0.2M, pH. . . minutes at room

temperature. The mixture was then passed over a Sephadex G-25 column (0.7.times.45 cm) to separate the activated **oligonucleotide** -DSS from the excess DSS. The **oligonucleotide**-DSS was then frozen immediately and lyophilized to dryness. A solution of **polyamine** in 0.33M NaOAc (approximately 6 mg **polyamine** in 300 ul 0.33M NaOAc, pH 5.2, final solution pH 6-8.0) was added to the dried **oligonucleotide**-DSS, and this mixture was allowed to react overnight at room temperature. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugates** (the larger the **polyamine**, the slower the migration) versus the **oligonucleotide** alone. (Gel: 313-107)

DETD **Polyamine conjugates** of the invention are assessed for their resistance to serum nucleases by incubation of the **oligonucleotides** in media containing various concentrations of fetal calf serum. Labeled **oligonucleotides** are incubated for various times, treated with protease K and then analyzed by gel electrophoresis on 20% polyacrylamide-urea denaturing gels. . . phosphor-imaging. Autoradiograms are quantitated by laser densitometry. Based upon the location of the modifications and the known length of the **oligonucleotide** it is possible to determine the effect of the particular modification on nuclease degradation. For the cytoplasmic nucleases, a HL60 cell line is used. A post-mitochondrial supernatant is prepared by differential centrifugation and the labeled **oligonucleotides** are incubated in this supernatant for various times. Following the incubation, **oligonucleotides** are assessed for degradation as outlined above for serum nucleolytic degradation. Autoradiography results are quantitated for comparison of the unmodified and the modified **oligonucleotides**. The t.sub.1/2 are set forth below.

DETD The **polyamine** functionalized **oligonucleotide** was prepared in accordance with Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugates** (the larger the **polyamine**, the slower the migration) versus the **oligonucleotide** alone. (Gel: 353-35).

DETD **Oligonucleotides** were functionalized as described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugates** (the larger the **polyamine**, the slower the migration) versus the **oligonucleotide** alone. (Test run 1 Gel, 313-82; Test run 2 Gel, 285-138; Test run 3 Gel, 353-57)

DETD C. Preparation of Biotin Functionalized **Oligonucleotide Polyamine Conjugate**

DETD To further characterize the **oligonucleotide polyamine conjugate,** biotin was attached to the **free amines** made available by the **polyamines** attached in Example 4-A-4-b. About 10 O.D. units (A.sub.260) of Oligomers A(i) and A(ii) (approximately 58 nmoles) were dried in a microfuge tube. The **oligonucleotide polyamine conjugate** was rehydrated in 400 ul of 0.2M NaHCO.sub.3 (pH 8.1) buffer and D-biotin-N-hydroxysuccinimide ester (approximately 5.0 mgs biotin for the 1,6 Diaminohexane **conjugate,** 8.0 mgs for the Diethylenetriamine) (Sigma) was added followed by 200 ul of DMF. The solution was left to react. . .

DETD The **oligonucleotide** was functionalized with **polyamines** as described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the

polyamine conjugates (the larger the **polyamine**
, the slower the migration) versus the **oligonucleotide** alone.
(Gel: 313-112)

DETD The **oligonucleotide** was functionalized as described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugates** (the larger the **polyamine**, the slower the migration) versus the **oligonucleotide** alone. (Gel: 313-97)

DETD The **polyamine** functionalized **oligonucleotide** was prepared in accordance with Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 397-85)

DETD The **polyamine** functionalized **oligonucleotide** was prepared in accordance with the procedures described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 397-85)

DETD The **polyamine** functionalized **oligonucleotide** is prepared in accordance with methods described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 397-85)

DETD The **polyamine** functionalized **oligonucleotide** is prepared in accordance with methods described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 353-156)

DETD The **polyamine** functionalized **oligonucleotide** is prepared in accordance with methods described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 397-85)

DETD The **polyamine** functionalized **oligonucleotide** is prepared in accordance with methods described in Example 4-A-1-b. The resulting **polyamine-oligonucleotide conjugate** was characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Gel analysis showed progressively slower migration times for the **polyamine conjugate** versus the **oligonucleotide** alone. (Gel: 353-149)

DETD The resulting **polyamine-oligonucleotide conjugates** were characterized by reverse phase HPLC and a 20% denaturing gel. Solvent A was 50 mM TEAA, solvent B was. . .

DETD Preparation of **Polyamine Conjugated Oligonucleotide**

DETD **Conjugation** of **Polyamines** to Abasics Sites Containing **Oligonucleotides**

```
=> d bib abs hitstr l10 7

L10  ANSWER 7 OF 18  HCAPLUS  COPYRIGHT 2000 ACS
AN   1998:202641  HCAPLUS
DN   128:266977
TI   Complexes of nucleic acid and polylysine conjugated with
     non-charged residues and recognition signals for the transfection of cells
IN   Midoux, Patrick; Erbacher, Patrick; Roche-Degremont,
     Annie-Claude; Monsigny, Michel
PA   I.D.M. Immuno-Designed Molecules, Fr.
SO   U.S., 53 pp. Cont.-in-part of U.S. 505,068, abandoned.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
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PI   US 5733762        A    19980331       US 1996-741678   19961031
     FR 2719316        A1   19951103       FR 1994-5174     19940428
     FR 2719316        B1   19960531
     US 5595897        A    19970121       US 1994-288681   19940810
     CA 2187629        AA   19951109       CA 1995-2187629  19950424
PRAI FR 1994-5174       19940428
     US 1994-288681     19940810
     US 1995-505068     19950721
AB   A compd. consisting essentially of polylysine with the free amino
     functions conjugated to non-charged residues and recognition signals is
     provided.  Non-charged residues may consist of gluconalactone, and the
     recognition signals are at least one member of the group consisting of
     galactoside, mannoside, fucoside, Lewisx, Lewisb, oligomannoside,
     oligolactosamine saccharides, and peptide atrial natriuretic
     peptide (ANP).  The conjugated polylysine contains .gtoreq.30%
     unsubstituted free amino functions.  HepG2 (human hepatocarcinoma) cells
     are efficiently transfected by the substituted polylysine contg. 58 .+-.
     12% gluconoyl residues with an efficiency .apprx.300-fold higher than with
     the plasmid DNA alone.  Polylysine substituted by a few gluconoyl residues
     are not effective for obtaining good transfection; those with too many
     residues are slightly effective for transfection.
IT   50-99-7D, D-Glucose, conjugates with polylysine 58-86-6D
     , Xylose, conjugates with polylysine 59-23-4D, D-Galactose,
     conjugates with polylysine 63-42-3D, Lactose, conjugates with
     polylysine 89-67-8D, conjugates with polylysine 90-80-2D
     , Gluconolactone, conjugates with polylysine 131-48-6D,
     N-Acetylneuraminic acid, conjugates with polylysine 147-81-9D,
     Arabinose, conjugates with polylysine 1069-03-0D,
     2-keto-3-Deoxyoctonic acid, conjugates with polylysine 1113-83-3D
     , N-Glycolylneuraminic acid, conjugates with polylysine 2073-35-0D
     , L-Iduronic acid, conjugates with polylysine 2438-80-4D,
     Fucose, conjugates with polylysine 3458-28-4D, D-Mannose,
     conjugates with polylysine 3615-41-6D, Rhamnose, conjugates with
     polylysine 5336-08-3D, D-Ribonolactone, conjugates with
     polylysine 6556-12-3D, Glucuronic acid, conjugates with
     polylysine 25104-18-1D, Polylysine, conjugates with noncharged
     residues and recognition signals 32181-59-2D, N-
     Acetyllactosamine, conjugates with polylysine 38000-06-5D
     , Polylysine, conjugates with noncharged residues and recognition signals
     56570-03-7D, Lewis a, conjugates with polylysine
     85637-73-6D, Atrial natriuretic peptide, conjugates with
     polylysine 117660-12-5D, Lewis b hexasaccharide, conjugates with
     polylysine 205534-18-5D, conjugates with polylysine
     RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
     (Uses)
        (complexes of nucleic acid and polylysine conjugated with
        non-charged residues and recognition signals for the transfection of
        cells)
RN   50-99-7  HCAPLUS
CN   D-Glucose (8CI, 9CI)  (CA INDEX NAME)
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=> d bib abs hitstr l10 14

L10 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:58122 HCAPLUS
DN 124:108913
TI Novel nucleic acid/substituted **polyamine complexes,** method for preparing same and use thereof for cell transfection
IN **Midoux, Patrick;** Erbacher, Patrick; Roche-Degremont, Annie-Claude; **Monsigny, Michel**
PA I.D.M. Immuno-Designed Molecules, Fr.
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9530020	A1	19951109	WO 1995-FR535	19950424
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	FR 2719316	A1	19951103	FR 1994-5174	19940428
	FR 2719316	B1	19960531		
	US 5595897	A	19970121	US 1994-288681	19940810
	CA 2187629	AA	19951109	CA 1995-2187629	19950424
	AU 9524128	A1	19951129	AU 1995-24128	19950424
	AU 695056	B2	19980806		
	EP 753070	A1	19970115	EP 1995-918049	19950424
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

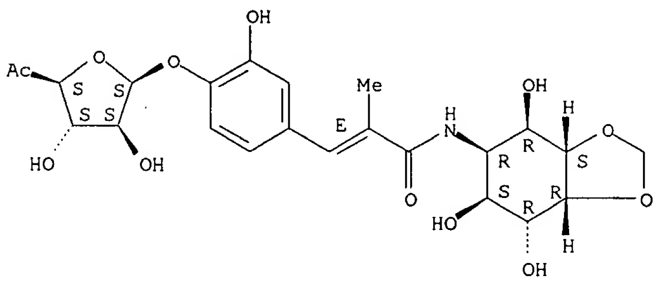
PRAI FR 1994-5174 19940428
US 1994-288681 19940810
WO 1995-FR535 19950424
AB A polymer consisting of monomers contg. free NH3+ groups, the free NH3+ functions being substituted in a ratio of at least 10%, advantageously 45-70% and particularly 60%, by uncharged residues causing a redn. in pos. charges relative to the unsubstituted polymer, is described. A **complex** consisting of at least one neg. charged nucleic acid and the described pos. charged polymer, and use of the **complex** for transfection of cells, are claimed. The substitution of the NH3+ groups reduces the pos. charge of the polymer and facilitates dissocn. of nucleic acid within cells. The group conjugated to the amino group is not a recognition signal for a cell membrane receptor, but a fraction of the remaining amino groups may be conjugated to such a moiety to facilitate uptake of the nucleic acid/polymer **complex** by cells. Thus, polylysine was reacted with D-gluconolactone to produce polylysine in which .apprx.60% of the amino groups were masked with the sugar. This conjugates was further derivatized with lactose or with biotin. The polylysine-gluconic acid-lactose conjugate was **complexed** with a plasmid contg. a luciferase gene. HepG2 cells were efficiently transfected using this **complex**. The effects of polylysine substitution on transfection efficiency were examd.
IT **9002-06-6,** Thymidine kinase
RL: MSC (Miscellaneous)
(gene for herpes simplex; novel nucleic acid/substituted **polyamine complexes** and their use for cell transfection)
RN 9002-06-6 HCAPLUS
CN Kinase (phosphorylating), thymidine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **1404-04-2,** Neomycin **6379-56-2**
RL: MSC (Miscellaneous)
(gene for resistance to; novel nucleic acid/substituted **polyamine complexes** and their use for cell

transfection)
RN 1404-04-2 HCAPLUS
CN Neomycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 6379-56-2 HCAPLUS
CN D-neo-Inositol, 5-deoxy-5-[[(2E)-3-[4-[(6-deoxy-.beta.-D-arabino-hexofuranos-5-ulos-1-yl)oxy]-3-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-1,2-O-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **9001-22-3**, .beta.-Glucosidase **9001-28-9**, Blood-coagulation factor IX **9014-00-0**, Luciferase **9025-05-2**, Cytosine deaminase **9026-93-1**, Adenosine deaminase **9029-73-6**, Phenylalanine hydroxylase **9031-11-2**, .beta.-Galactosidase **9036-22-0**, Tyrosine hydroxylase **9040-07-7**, Chloramphenicol acetyltransferase **9041-92-3**, .alpha.1-Antitrypsin **9061-61-4**, Nerve growth factor **113189-02-9**, Blood-coagulation factor VIII **125978-95-2**, Nitric oxide synthase
RL: MSC (Miscellaneous)
(gene for; novel nucleic acid/substituted **polyamine complexes** and their use for cell transfection)
RN 9001-22-3 HCAPLUS
CN Glucosidase, .beta.- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-28-9 HCAPLUS
CN Blood-coagulation factor IX (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9014-00-0 HCAPLUS
CN Luciferase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9025-05-2 HCAPLUS
CN Deaminase, cytosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9026-93-1 HCAPLUS
CN Deaminase, adenosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9029-73-6 HCAPLUS
CN Oxygenase, phenylalanine 4-mono- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9031-11-2 HCAPLUS
CN Galactosidase, .beta.- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9036-22-0 HCAPLUS
CN Oxygenase, tyrosine 3-mono- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9040-07-7 HCAPLUS
CN Acetyltransferase, chloramphenicol (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, .alpha.1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9061-61-4 HCAPLUS
CN Nerve growth factor (9CI) (CA INDEX NAME)

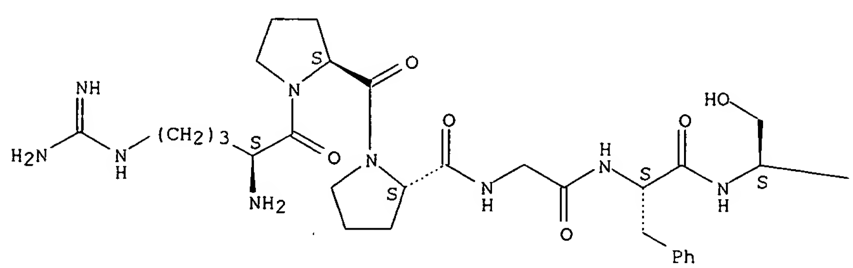
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 113189-02-9 HCAPLUS
CN Blood-coagulation factor VIII, procoagulant (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 125978-95-2 HCAPLUS
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **58-82-2D**, Bradykinin, conjugates with substituted polyamines **58-85-5D**, Biotin, conjugates with substituted polyamines **59-30-3D**, Folic acid, conjugates with substituted polyamines **63-42-3D**, Lactose, conjugates with polylysine-gluconic acid conjugate, **complexes** with DNA **135-16-0D**, conjugates with substituted polyamines **526-95-4D**, D-Gluconic acid, conjugates with polylysine, **complexes** with DNA **541-15-1D**, Carnitine, conjugates with substituted polyamines **581-05-5D**, .alpha.-Melanotropin (pig), conjugates with substituted polyamines **25104-18-1D**, Poly-L-lysine, conjugates, **complexes** with DNA **38000-06-5D**, Poly-L-lysine, conjugates, **complexes** with DNA **40077-57-4D**, Vasoactive intestinal octacosapeptide (pig), conjugates with substituted polyamines **59880-97-6D**, conjugates with substituted polyamines **91917-63-4D**, Atriopeptin-28 (human reduced), conjugates with substituted polyamines **94120-04-4D**, conjugates with substituted polyamines **104068-33-9D**, conjugates with substituted polyamines **118850-72-9D**, conjugates with substituted polyamines **130014-46-9D**, conjugates with substituted polyamines **153604-57-0D**, conjugates with substituted polyamines **172787-60-9D**, conjugates with substituted polyamines **172787-61-0D**, conjugates with substituted polyamines **172787-62-1D**, conjugates with substituted polyamines **174828-76-3D**, conjugates with substituted polyamines
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(novel nucleic acid/substituted **polyamine complexes** and their use for cell transfection)
RN 58-82-2 HCAPLUS
CN Bradykinin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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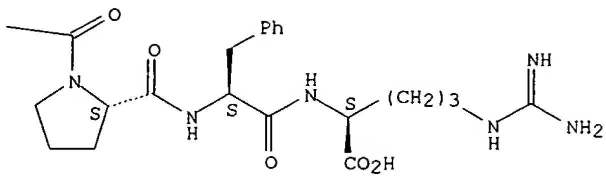
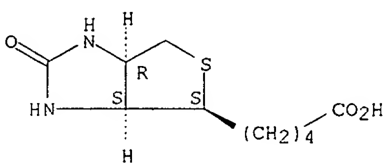


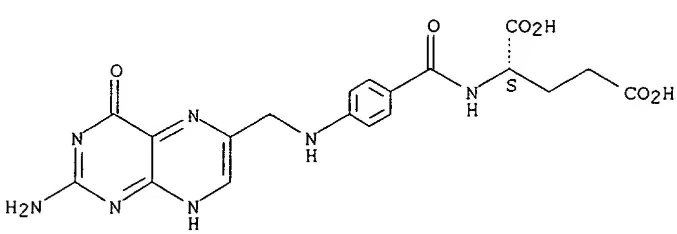
RN 58-85-5 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



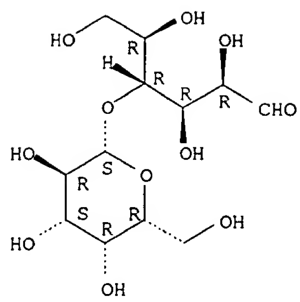
RN 59-30-3 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



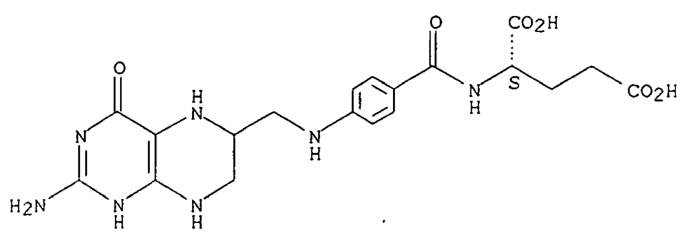
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



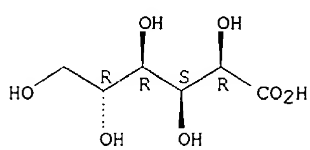
RN 135-16-0 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



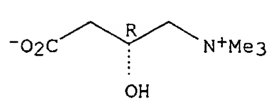
RN 526-95-4 HCAPLUS
CN D-Gluconic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 541-15-1 HCAPLUS
CN 1-Propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl-, inner salt, (2R)-(9CI) (CA INDEX NAME)

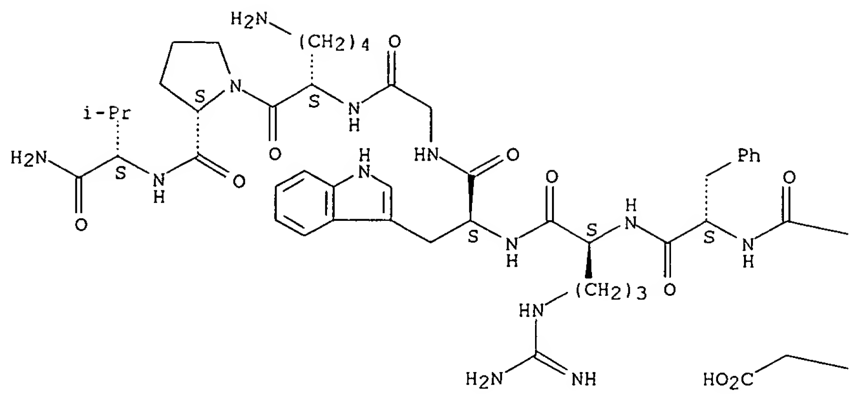
Absolute stereochemistry.



RN 581-05-5 HCAPLUS
CN .alpha.-Melanotropin (swine) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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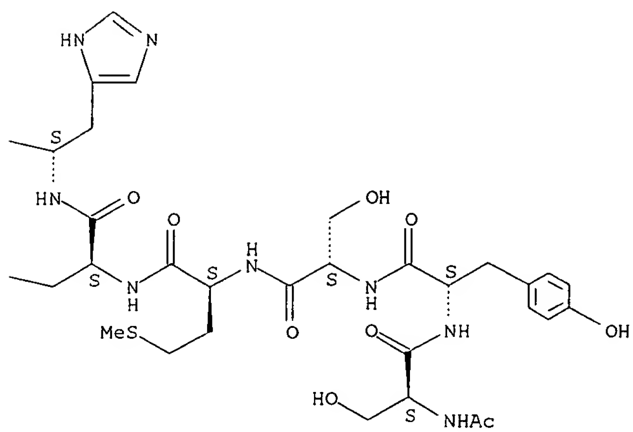
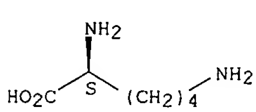


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

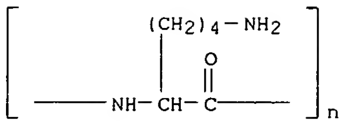
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



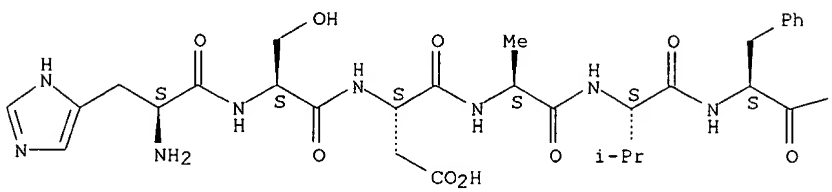
RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RN 40077-57-4 HCAPLUS
CN Vasoactive intestinal octacosapeptide (swine) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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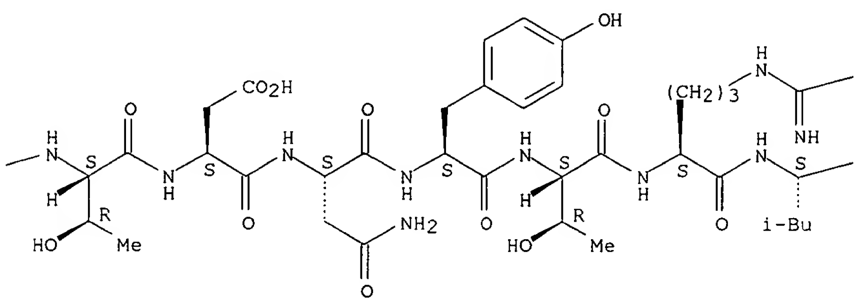

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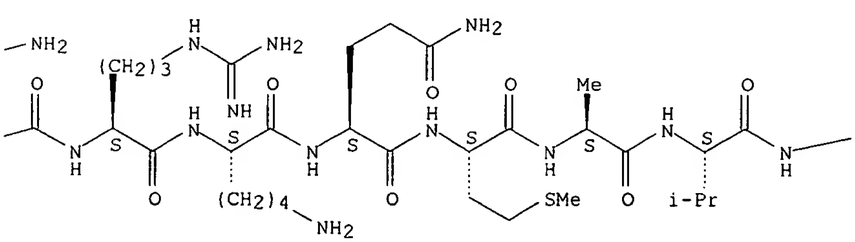

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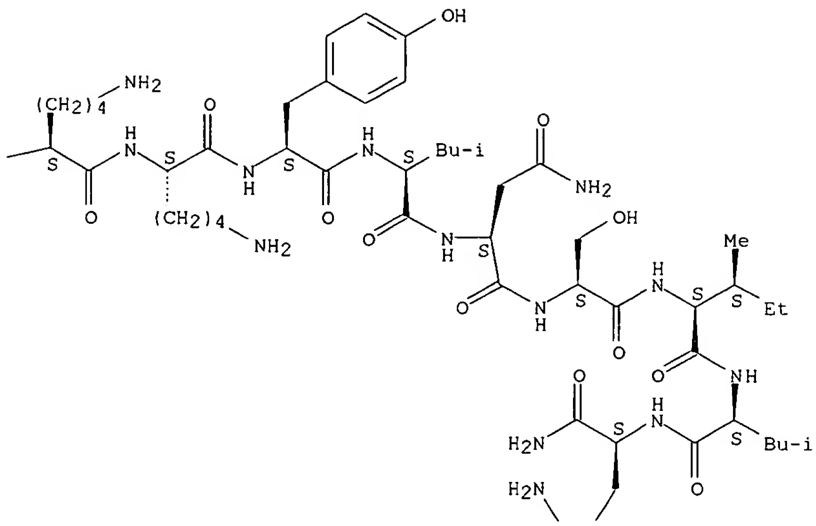
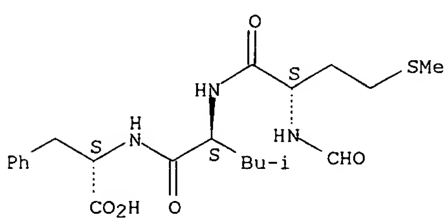


PAGE 2-D

RN 59880-97-6 HCAPLUS
CN L-Phenylalanine, N-formyl-L-methionyl-L-leucyl- (9CI) (CA INDEX NAME)

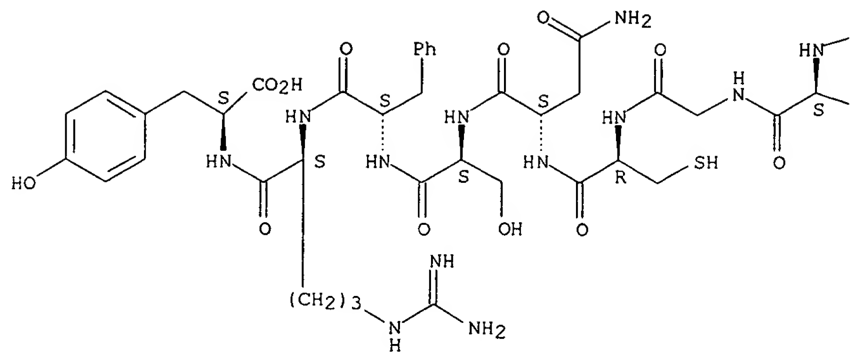
Absolute stereochemistry.



RN 91917-63-4 HCAPLUS
CN Atrial natriuretic peptide-28 (human reduced) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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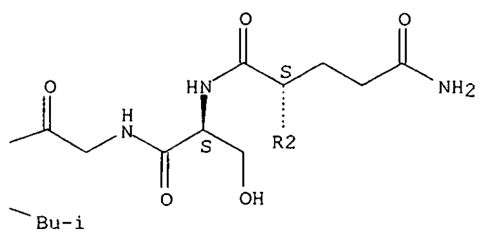
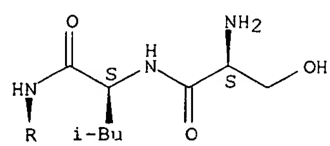
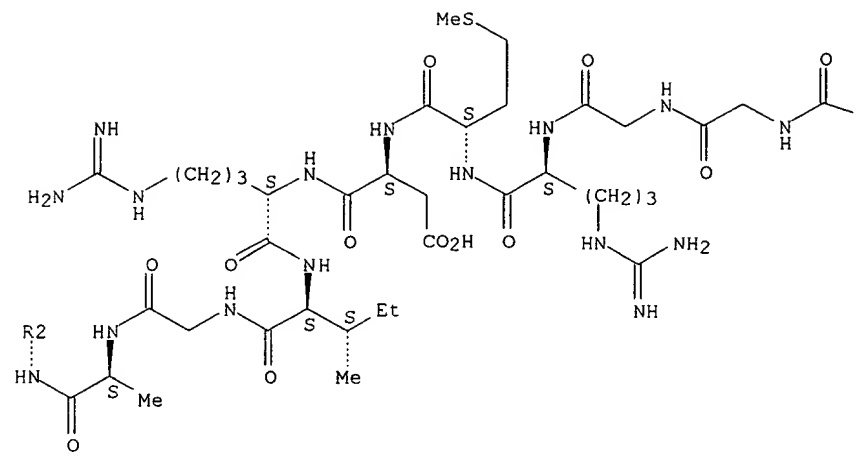


PAGE 2-A



PAGE 3-A



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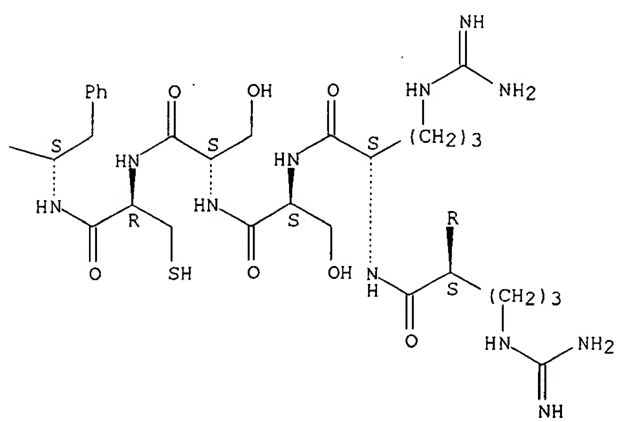
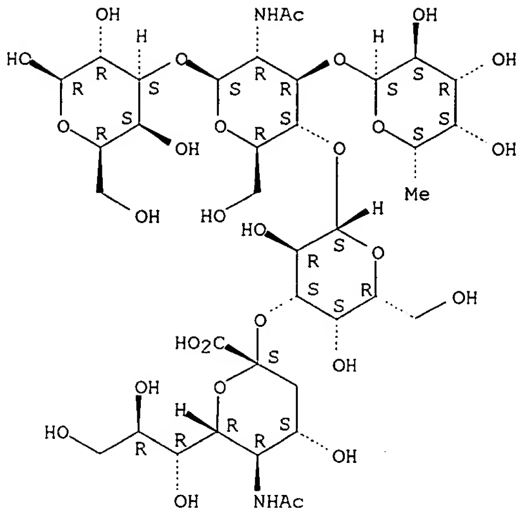


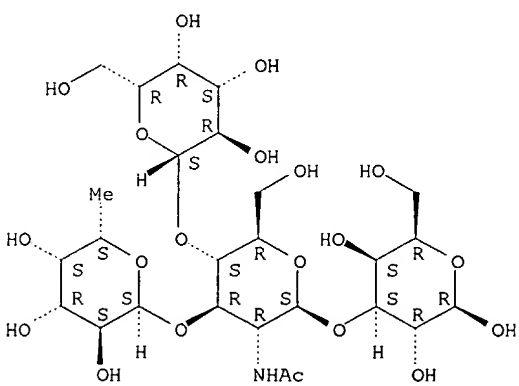
RN 94120-04-4 HCAPLUS
CN .beta.-D-Galactopyranose, O-(N-acetyl-.alpha.-neuraminosyl)-(2.fwdarw.3)-O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-[6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.3)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 104068-33-9 HCAPLUS
CN .beta.-D-Galactopyranose, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.3)-O-[.beta.-D-galactopyranosyl-(1.fwdarw.4)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)- (9CI) (CA INDEX NAME)

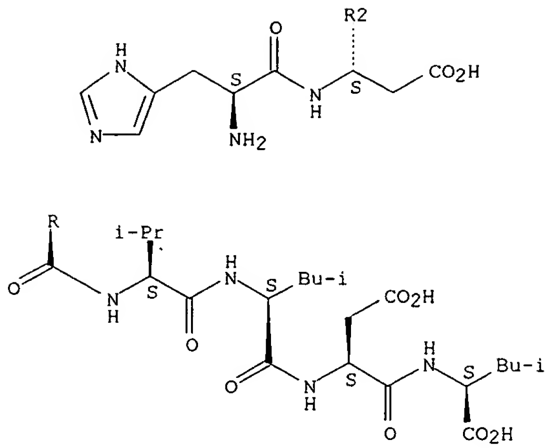
Absolute stereochemistry.



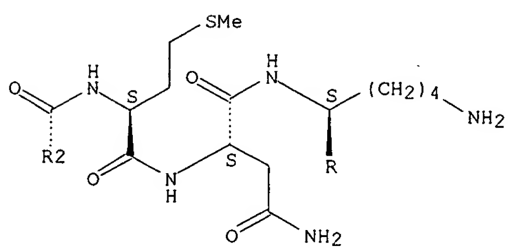
RN 118850-72-9 HCAPLUS
CN L-Leucine, L-histidyl-L-.alpha.-aspartyl-L-methionyl-L-asparaginyl-L-lysyl-L-valyl-L-leucyl-L-.alpha.-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



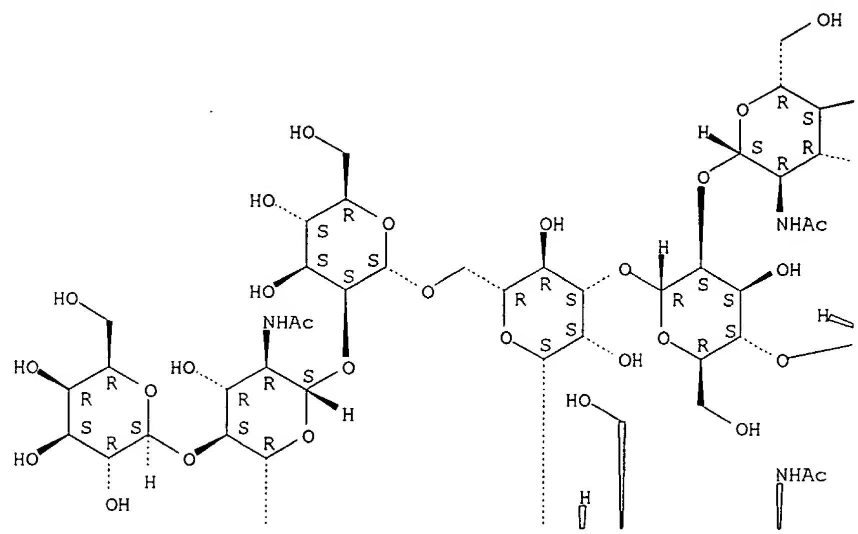
PAGE 2-A



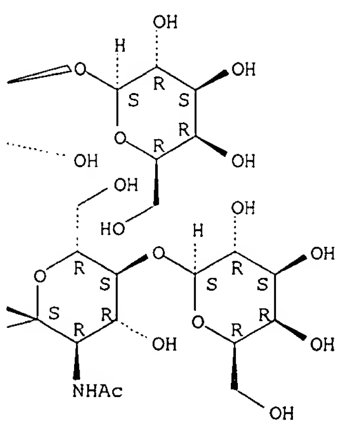
RN 130014-46-9 HCAPLUS
CN .beta.-D-Glucopyranose, O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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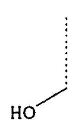

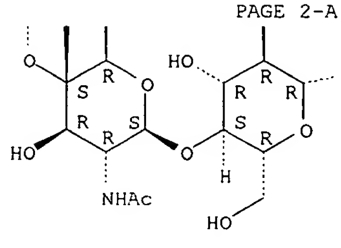

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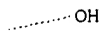

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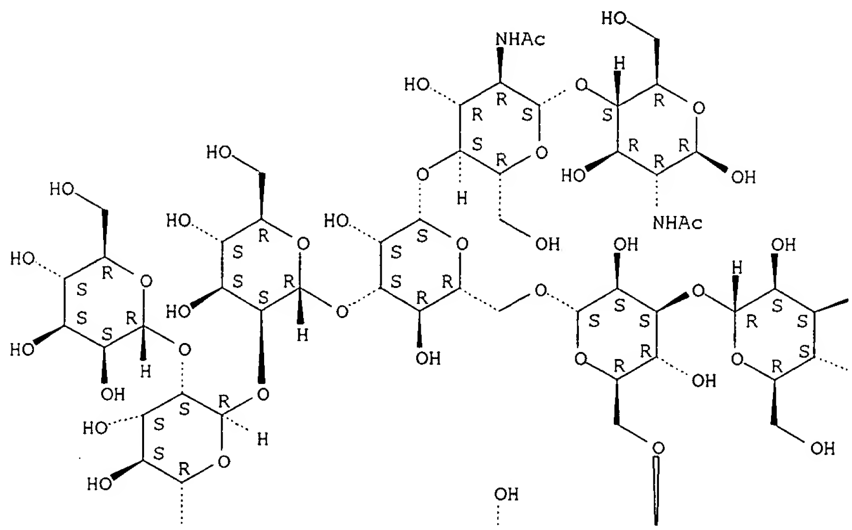
Absolute stereochemistry.

PAGE 1-A



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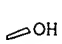

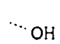

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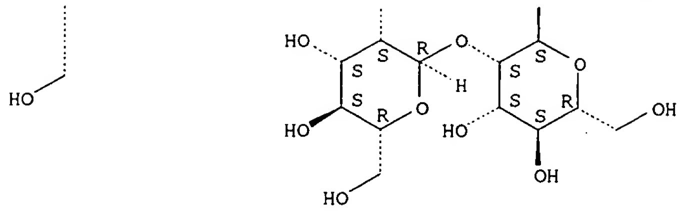

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Absolute stereochemistry.

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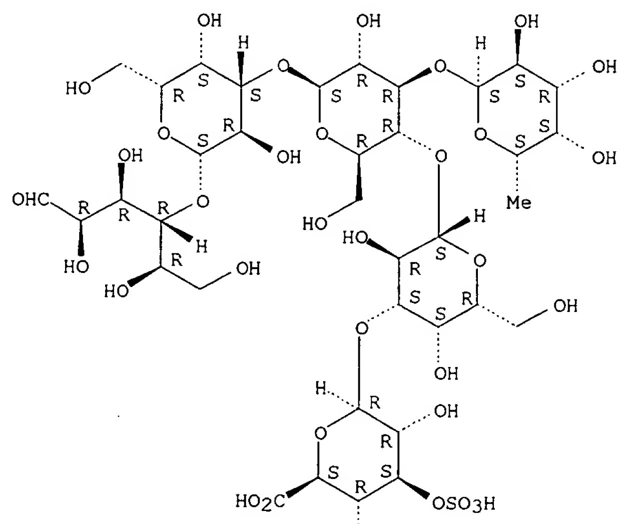

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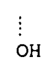

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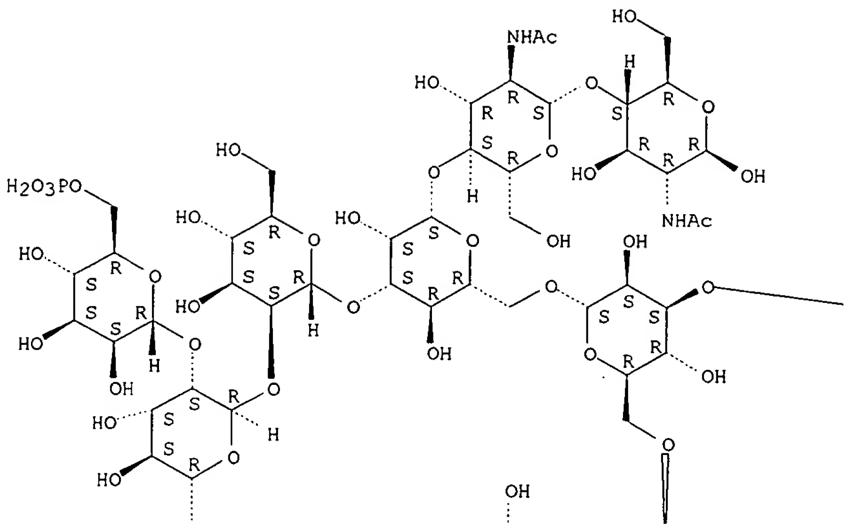
Absolute stereochemistry.

PAGE 1-A



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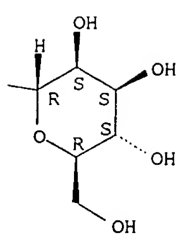

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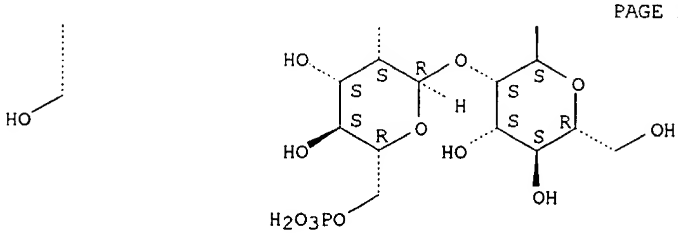

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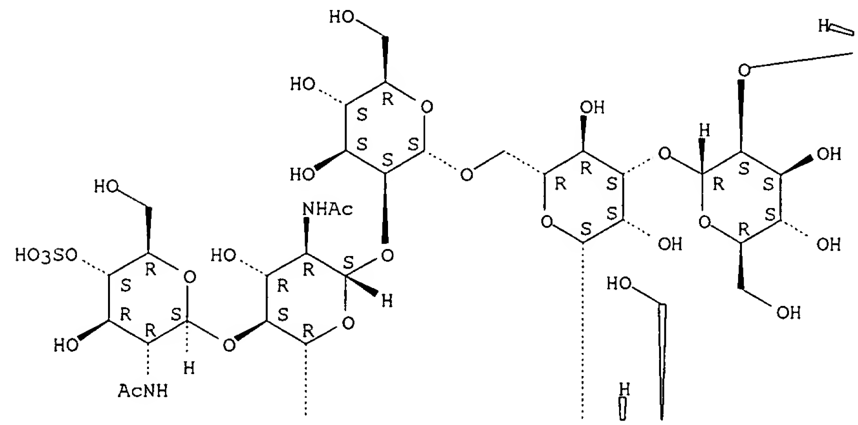
(acetylamino)-2-deoxy-4-O-sulfo-.beta.-D-glucopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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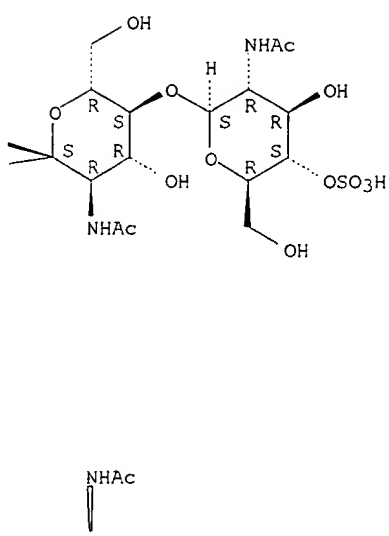

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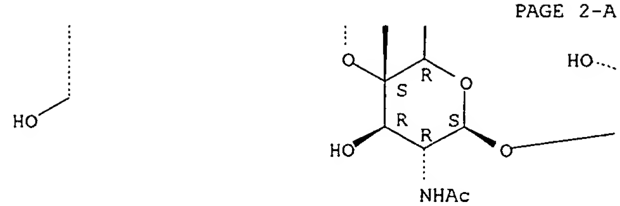

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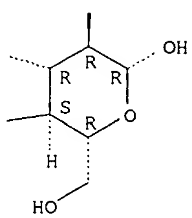

RN 174828-76-3 HCAPLUS
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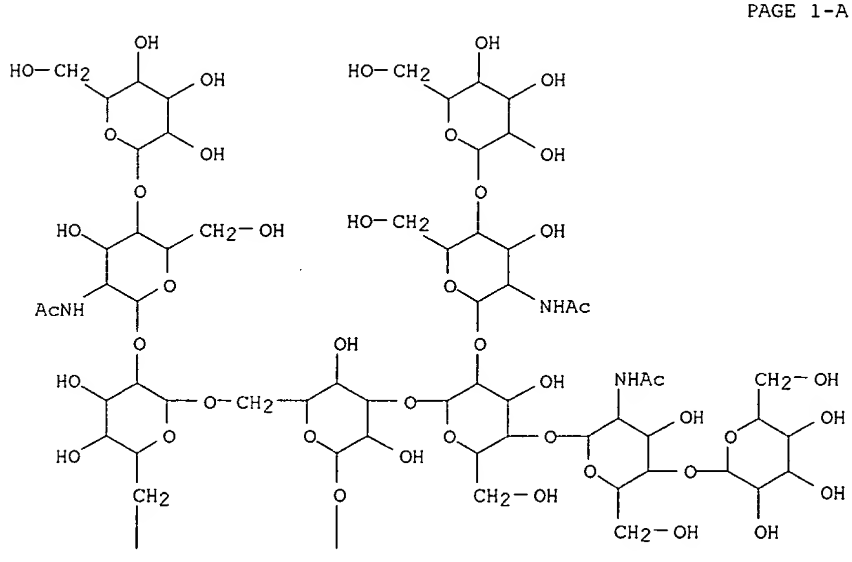
PAGE 1-A



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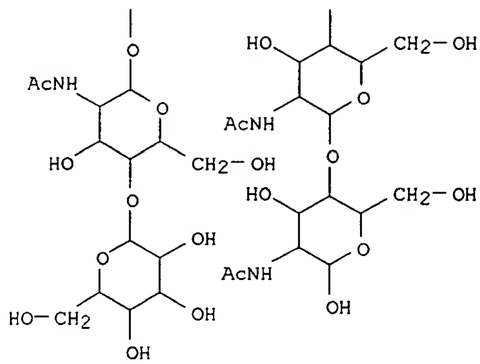

=> d bib abs l73 40

L73 ANSWER 40 OF 57 USPATFULL
AN 97:38613 USPATFULL
TI Glycosylated steroid derivatives for transport across biological **membranes** and process for making and using same
IN Kahne, Daniel E., Princeton, NJ, United States
Kahne, Suzanne W., Princeton, NJ, United States
Sofia, Michael J., Laurenceville, NJ, United States
Hatzenbuhler, Nicole T., Kendall Park, NJ, United States
PA Trustees of Princeton University, Princeton, NJ, United States (U.S. corporation)
Transcell Technologies, Inc., Monmouth Junction, NJ, United States (U.S. corporation)
PI US 5627270 19970506
AI US 1994-264488 19940623 (8)
RLI Continuation-in-part of Ser. No. US 1994-230685, filed on 20 Apr 1994 which is a continuation-in-part of Ser. No. US 1992-989667, filed on 14 Dec 1992 which is a continuation-in-part of Ser. No. US 1991-806985, filed on 13 Dec 1991, now patented, Pat. No. US 5338837
DT Utility
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Lee, Howard C.
LREP Lowe, Price, LeBlanc & Becker
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 22 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 3296
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel glycosylated steroid derivatives for facilitating the transport of compounds across biological **membranes**, either in admixture or as conjugates, are disclosed. A novel process for efficient synthesis of these glycosylated steroid derivatives, using activated glycosyl sulfoxide intermediates is provided. Methods for the permeabilization of **membranes** and the enhancement of the activity of predetermined compounds are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L73 ANSWER 40 OF 57 USPATFULL
TI Glycosylated steroid derivatives for transport across biological **membranes** and process for making and using same
AB Novel glycosylated steroid derivatives for facilitating the transport of compounds across biological **membranes**, either in admixture or as conjugates, are disclosed. A novel process for efficient synthesis of these glycosylated steroid derivatives, using activated glycosyl sulfoxide intermediates is provided. Methods for the permeabilization of **membranes** and the enhancement of the activity of predetermined compounds are also provided.
SUMM . . . novel glycosylated steroid derivatives. These derivatives have a variety of uses, including but not limited to the general permeabilization of **membranes**, such as biological **membranes** (e.g., cellular, mucosal, gastrointestinal, blood-brain barrier, and the like). In particular, the present derivatives are useful in facilitating the transport of molecules across biological **membranes**. The facilitation is achieved by combining the present derivatives with the molecules of interest, either as a conjugate comprising the. . .
SUMM Effective strategies to enhance absorption of therapeutically-significant-molecules across **membranes**, such as mucosal **membranes**, cellular **membranes**, nuclear **membranes**, and the like, could enhance the efficacy of many known drug preparations that are poorly absorbed regardless of the method of administration. Such strategies to enhance trans-**membrane** absorption or **penetration** could be

particularly useful for therapeutically-significant-compounds that are administered across the skin and mucosal tissues, including mucosal tissues of the. . . .

SUMM The basic structural unit of biological **membranes** is a phospholipid bilayer, in which are embedded proteins of various size and composition. The surfaces of the phospholipid bilayer,. . . . the hydrophilic heads of the phospholipids; the interior of the bilayer is comprised of the fatty acyl hydrophobic tails. The **membrane** proteins may be involved in transport processes and also may serve as receptors in cellular regulatory mechanisms or signal transduction.

SUMM Natural mechanisms for traversal of biological **membranes** include passive diffusion, facilitated diffusion, active transport, receptor-mediated endocytosis and pinocytosis. Passive diffusion works best for small molecules that are lipid-soluble. However, biological **membranes** are essentially impermeable to most water-soluble molecules, such as nucleosides, amino acids, proteins, and other hydrophilic, therapeutically-significant-molecules. Such molecules enter cells via some type of carriermediated transport system in which specific entities facilitate traversal of the **membrane**. Natural carriers for facilitating traversal of the **membrane** are of limited utility, however, as such carriers will accept substrates of only a predetermined molecular configuration. Many therapeutically-significant-compounds are not efficiently absorbed because they are neither lipophilic enough to diffuse passively across cell **membranes** nor possess the structural features recognized by the natural transport systems.

SUMM Strategies to enhance the uptake of therapeutically-significant-molecules across biological **membranes** have been investigated previously and fall into two broad categories. The first category includes all strategies in which the structure. . . . by making the compound itself more lipophilic or by conjugating the compound to other entities known to interact with phospholipid **membranes**. The common goal has been to increase passive diffusion across the **membrane** by lowering the energy barrier to diffusion and/or by increasing the local concentration of the compound at the **membrane** surface.

SUMM . . . requires traversal of the blood-brain barrier, a capillary including system with unique morphological characteristics, which acts as a system-wide cellular **membrane** separating the brain interstitial space from the blood. Like other biological **membranes**, the bloodbrain barrier is relatively impermeable to many hydrophilic, therapeutically-significant-compounds. The strategies which have been developed for targeting compounds to. . . .

SUMM . . . which the therapeutically-significant-compound is administered to specific body surfaces as an admixture with other molecules that are known to permeabilize **membranes**. For example, several investigators have attempted to mix insulin with adjuvants, such as bile salts, which might enhance nasal insulin. . . .

SUMM . . . present invention may be used effectively in a strategy for enhancing the uptake of a second compound through a particular **membrane**, including the two broad categories discussed above. Indeed, it has been discovered that the instant derivatives can interact with a wide variety of **membranes**, including biological phospholipid **membranes**, thereby possessing the potential to enhance the penetration of therapeutically-significant-compounds through such **membranes**.

SUMM . . . been shown by the inventors to be more effective than the parent, nonglycosylated steroids in permeabilizing both artificial and biological **membranes**. The novel, glycosylated steroid derivatives of the present invention, therefore, have been found to increase the delivery of therapeutically-significant-compounds across a variety of **membranes**. The enhanced transport is facilitated by combining the instant derivatives with the therapeutically-significant-compounds, either as admixtures or as conjugates therewith.

SUMM . . . to novel, facially-amphiphilic, glycosylated steroid derivatives which have been found to be soluble in both hydrophilic aqueous media and hydrophobic **membrane**-like environments. These unique solubility properties permit the glycosylated steroid derivatives to facilitate the transport of other molecules across biological **membranes**, including the blood brain barrier. It

is, therefore, contemplated that the glycosylated steroid derivatives of the present invention can be. . . gastric, intestinal, endometrial, cervical, vaginal or colonic epithelium; the oropharynx, ear canal, respiratory tract, nasopharynx, urethra, urinary bladder, and tympanic **membrane**. Alternatively, the glycosylated steroid derivatives of the present invention may be administered in admixture with the glycosylated steroid derivative/therapeutically-significant-molecule conjugate (hereinafter referred to as the "derivative-compound-conjugate" or simply "conjugate") to further enhance facilitation of trans-surface and trans-**membrane** transport.

SUMM . . . independently of the other. Hence, the present invention provides methods for facilitating the transport of any therapeutically-significant-compound across a biological **membrane**, either in admixture with a glycosylated steroid derivative of the present invention or in the form of a derivative-compound-conjugate. Alternatively, a method is provided for further enhancing trans-**membrane** transport of the derivative-compound-conjugate by administering the derivative-compound-conjugate in admixture with a glycosylated steroid derivative of the present invention, which. . .

SUMM . . . (any other steroid hydroxyl groups which are not to be glycosylated are protected by standard methods) in the presence of 2,6-di-tert-butyl4-**methylpyridine** in toluene solvent (for formation of alpha,alpha glycosidic linkages) or in propionitrile solvent (for the formation of beta,beta glycosidic linkages),. . .

SUMM Preferred for their ability to permeabilize biological **membranes** are those compounds of Formula (I) in which A is OH, OR.sup.6, O--CO--R.sup.9, OCOC.sub.6 H.sub.5, OCOC.sub.6 H5--pOMe, NH.sub.2 ; "a". . .

SUMM Preferred for their ability to permeabilize biological **membranes** are:

DETD . . . diagnostic, prophylactic or therapeutic interest across body surfaces and/or into cells requires the traversal of one or more semipermeable biological **membranes**. The compounds of this invention are useful in permeabilizing biological **membranes**, thereby assisting body surface and/or **membrane** transversal of therapeutically-significant-compounds. In one embodiment, the therapeutically-significant-compound is administered in admixture with a glycosylated steroid derivative of the present invention. In another embodiment, trans-surface and/or trans-**membrane** transport is facilitated by administering the therapeutically-significant-compound in the form of a derivative-compound-conjugate in which the compound of interest is. . . wide variety of compounds. As a result, many therapeutic applications for the compounds of the present invention may be contemplated. **Membrane** permeable therapeutic agents could be used in the treatment of a wide variety of illnesses including AIDS and other chronic. . . rheumatoid arthritis. The ability of the novel glycosylated steroid derivatives of the present invention to interact with, and/or permeabilize, biological **membranes**, is believed to result from the compounds' facial amphiphilicity. The glycosylated surface of the derivatives is hydrophilic; the non-glycosylated surface. . .

DETD . . . believe (although not wishing to be limited by theory) that the novel glycosylated steroid derivatives of the present invention permeabilize **membranes** by self-associating to form small, reverse micelles, with their hydrophobic surfaces exposed to the lipids within the **membranes**. These reverse micelles may function as water-filled pores, allowing therapeutically-significant-compounds to pass through. Alternatively, the presence of these reverse micelles in the **membrane** may perturb **membrane** order enough to permit passage of the compounds of therapeutic significance.

DETD . . . of the present invention facilitate the transport of protons or other ions such as Ca.sup.2+, Na.sup.+ or K.sup.+ across biological **membranes**, indicating their use as potential antifungal or antibiotic agents.

DETD Thus, a drug therapy method is contemplated which utilizes glycosteroid-oligonucleotide conjugates for the effective delivery of antisense oligonucleotides across biological **membranes**. Most preferably bis-glycosylated steroid **membrane** permeation enhancers are conjugated to antisense oligonucleotide sequences known to

inhibit viral (e.g., HIV) replication to provide an effective anti-viral. . . vivo studies. The development of this technology which provides the reliable deliver of antisense oligonucleotides both across cellular and mucosal **membranes** promises to fulfill the long-awaited anticipated benefits of antisense oligonucleotide drug and gene therapy.

DETD . . . without linkers. The complement is synthesized for melting temperature experiments to determine the stability of the duplex before and after **conjugation** with the glycosylated steroid. The duplex is also desirable for NMR studies to confirm the presence of the amide linkage between the **oligonucleotide** and the steroid. The syntheses are carried out on an ABI **DNA** synthesizer using the solid-phase cyanoethylphosphoramidite triester coupling approach developed by Beaucage and Caruthers (S. L. Beaucage, M. H. Caruthers, Tet. Lett., 22, 1859-1862 (1981).) The final dimethoxytrityl ("DMTr") protecting group is left on. The **oligonucleotides** are then cleaved from the **polymer** support in NH.sub.4 OH at room temperature and fully deprotected after incubation at 55.degree. C. overnight. The hydrophobicity of the dimethoxytrityl protecting group allows easy purification of the desired **oligonucleotide** by reverse-phase HPLC. The purified oligomer is detritylated and isolated by ethanol precipitation.

DETD An amino linker can be introduced either at the 5'- or 3'-terminus of the **oligonucleotide**. As stated earlier, 5 because the synthesis of **DNA** is carried out in a 3'- to 5'-direction (the 3'-end is linked to a **polymer** support), it is more convenient to introduce an amino linker at the 5'-end of the **oligonucleotide**. Furthermore, the introduction of the linker can best be carried out using the phosphoramidite chemistry where the commercially available reagents. . . RP HPLC. The trifluoroacetyl protecting group is cleaved under the basic conditions required for cleavage of the oligomer from the **polymer** support. The selective cleavage of the MMTr group while the **oligonucleotide** is still attached to the **polymer** support allows **conjugation** of the glycosylated steroid using solid-phase chemistry.

DETD . . . the cleavage of the disulfide bridge and elimination of ethylenesulfide and carbon dioxide occurs (See Scheme 4) to afford the **free amino** group together with the removal of the cyanoethyl group from the internucleotide phosphate and the acyl groups from the nucleic. . .

DETD The **conjugation** of a glycosylated steroid to an amino-linked **oligonucleotide** can be carried out two ways: **conjugation** in solution or on a **polymer** support. Several reports have been published in the literature regarding the **conjugation** of biotin to **oligonucleotides** in solution (S. Agrawal, C. Christodoulou, M. J. Gait, Nucl. Acids Res., 14, 6227-6245 (1986); L. Wachter, J-A. Jablonski, K.. . . R. K. Gaur, Nucleosides and Nucleotides, 10, 895-909 (1991).) Thus, the N-hydroxysuccinimide derivative of biotin dissolved in DMF and the **oligonucleotide** dissolved in HEPES or Tris-HCl buffer are mixed together and stirred at room temperature from 1 to 24 hours. The resulting product is purified by RP (i.e., reverse phase) HPLC. One report has also been published on the **conjugation** reaction carried out on a **polymer** support (B. D. Gildea, J. M. Coull, H. Koster, Tet. Lett., 31, 7095-7098 (1990)).

DETD To achieve **conjugation** on a **polymer** support, the amino-linked **oligonucleotide** is prepared preferably using the Peninsula Labs reagent in which a MMTr group is present on the amino functionality. The **oligonucleotide** (still linked to CPG) is detritylated and treated with the N-hydroxysuccinimide derivative of the steroid of interest in CH.sub.3 CN/DIEA/H.sub.2. . .

DETD . . . 9, and 10, all single-stranded, are further tested in an antiviral assay and in their enhanced ability to cross cell **membranes**.

DETD . . . the protected glycosyl sulfoxide in toluene at -78.degree. C. followed by the addition of an acid scavenger such as 2,6-di-tert-butyl4-methyl **pyridine** (Aldrich Chemical Co.) in toluene and the nucleophile dissolved in toluene at -78.degree. C. After stirring for 15-30 minutes, the. . . .beta.,.beta. glycosidic

linkages are formed regardless of the solvent used for the reaction. Alternatively, the protected glycosyl sulfoxide, nucleophile and **pyridine** base are dissolved in propionitrile at -78.degree. C., followed by the addition of triflic anhydride at -78.degree. C. and the. . .

DETD . . . argon. 2,3,4,6-tetra-Obenzyl glucose sulfoxide (2.97 g, 4.57 mmol, 4.0 eq.), C3-ethylcarbonate cholic acid (0.563 g, 1.14 mmol, 1.0 eq.) and 2,6-di-tert-butyl-4-**methylpyridine** (0.936 g, 4.57 mmol, 4.0 eq.) are each dried by azeotroping each separately three times with toluene (15.0 ml). Triflic. . . added to the glycosyl sulfoxide dissolved in toluene (5.0 ml) at -78.degree. C. To this mixture is then added the **pyridine** base in toluene (5.0 ml). After five minutes, the cholic acid derivative, dissolved in methylene chloride (1.0 ml) and toluene. . .

DETD . . . sulfoxide (1.012 g, 1.45 mmol, 4.0 eq.), C3-O-benzoyl cholic acid methylester (0.191 g, 0.364 mmol, 1.0 eq.) and 2,6-di-tert-butyl-4 methyl **pyridine** (0.179 g, 0.874 mmol, 2.4 eq.) are azeotroped together three times from toluene (20 ml). After removing the toluene under. . .

DETD A solution of methyl cholate (42.2 g, 0.1 mol), p-anisoyl chloride (20 mL, 0.133 mol) and DMAP (1 g) in **pyridine** (500 mL) is stirred and refluxed for 8 h. Additional p-anisoyl chloride (10 mL, 0.67 mol) is addded and stirred. . .

DETD . . . toluene (300 mL) is added dropwise. After 15 min of stirring, a solution of dried (by azeotropic distillation with toluene) 2,6-di-ter-butyl-4-methyl-**pyridine** (30.8 g, 0.150 mol) in toluene (100 mL) is added to the reaction mixture and stirred for 10 min at. . .

DETD To a cooled (0.degree. C.) solution of methyl cholate derivative 8 (13 g, 8.87 mmol) and **pyridine** (2.5 mL, 31 mmol) in dichloromethane (50 mL), triflic anhydride is added and allowed to stir for 20 min. To. . .

DETD . . . the hydrogenation reaction allowed to proceed for another 24 h. The reaction mixture is then filtered through sand over a **membrane** filter and concentrated. The filtrate is then mixed with ethyl acetate to form a precipitate. (Some of the methanol solvent. . .

DETD . . . A second 24 h reaction period can then be initiated.) The reaction mixture is then filtered through sand over a **membrane** filter and concentrated. The filtrate is then mixed with ethyl acetate to form a precipitate. (Some of the methanol solvent. . .

DETD The amino compound 5 (340 mg, 0.23 mmol) is dissolved in **pyridine** (2 mL) and cooled to 0.degree. C. in an ice-bath. To this solution is added acetic anhydride (0.5 mL). The. . .

DETD . . . toluene (100 mL), is added dropwise. After 15 min of stirring, a solution of dried (by azeotropic distillation from toluene) 2,6-di-ter-butyl-4-methyl-**pyridine** (8.21 g, 40 mmol) in toluene (20 mL) is added to the reaction mixture and stirred for 10 min at. . .

DETD . . . triethylamine (3 mL) with stirring at 40.degree. C. for 1 h. The compound 2 (2.986 g, 2 mmol) and ethyl 1,2-dihydro-2-ethoxy-1-**quinolinecarboxylate** (EEDQ) (988 mg, 4 mmol) in ethylacetate (100 mL) are then added to this mixture, which is then heated under. . .

DETD . . . and further hydrogenation can be added and performed as warranted. The reaction mixture is then filtered through sand and a **membrane** filter and concentrated. The residue is precipitated with EtOAc and filtered. The precipitate is dissolved in 25 mL deionized water. . .

DETD . . . dry toluene is added triflic anhydride (1.66 mL, 9.8 mmol) at -78.degree. C. After 15 min. stirring at -78.degree. C., 2,6-di-t-butyl-4-**methylpyridine** (2 g, 9.8 mmol) in a small amount of toluene is added, followed by 2 (2 g, 4.4 mmol) in. . .

DETD To a solution of 6 (2.73 g, 6.4 mmol) in dry **pyridine** at 0.degree. C. is added methanesulfonyl chloride (0.6 mL, 7.7 mmol). The resulting mixture is stirred at 0.degree. C. for. . .

DETD . . . dry toluene is added triflic anhydride (1.05 mL, 9.8 mmol) at -78.degree. C. After 30 min. stirring at -78.degree. C., 2,6-di-t-butyl-4-**methylpyridine** (1.17 g, 5.7 mmol) in a small amount of toluene is added, followed by 7 (1.15 g, 2.6 mmol) in. . .

DETD A mixture of 2 (58 g, 0.138 mol), p-anisoyl chloride (31.9 mL) and DMAP (60 g) in **pyridine** is refluxed gently for 16 h. After removal of the solvent, the residue is dissolved in methylene chloride, washed consecutively. . . .

DETD . . . toluene is added triflic anhydride (5.9 mL, 35 mmol) at -78.degree. C. After 15 min. stirring at -78.degree. C., 2,5-di-t-butyl-4-methyl **pyridine** (7.1 g, 35 mmol) in 20 mL toluene is added, followed by the solution of 3 (7.74 g, 14 mmol,. . . .

DETD Methyl chenodeoxycholate (27 g, 61.5 mmol) is dissolved in 100 mL dichloromethane (DCM), **pyridine** (20 mL). **Dimethylaminopyridine** (DMAP) (1.22 g, 10 mmol) is then added. The reaction mixture is chilled to 0.degree. C., and methanesul-fonyl chloride (7.5. . . .

DETD . . . toluene (150 mL) is treated dropwise at -78.degree. C. with triflic anhydride (1.06 mL, 6.25 mmol) in toluene (10 mL). 2,6-Diisopropyl-4-methyl-**pyridine** (1.3 g, 6.25 mmol) in toluene (10 mL) is added dropwise. Methyl 3-azido-deoxycholate 2 (2.16 g, 5 mmol) in toluene/dichloromethane. . . .

DETD The sulfoxide 12 (0.96 g, 2.5 mmol), the methyl 3.beta.-azido-cholate 13 (2.5 mmol), and 2,6-diisopropyl-4-methyl-**pyridine** (0.63 g, 3.3 mmol) are dissolved in 100 mL of toluene and chilled to -78.degree. C. under Ar. Triflic anhydride. . . .

DETD . . . sequence (SEQ. ID NO:1) synthesized on a 1.0 .mu.mole scale using the C.sub.6 -CEP reagent is detritylated on an ABI **DNA** synthesizer using TCA. The top portion of the column is removed and the CPG support is poured into a reaction. . . . is filtered and washed three times with acetonitrile:water (8:1,v:v) followed by acetonitrile (3 times). The cholic acid-ASAS (SEQ. ID NO:2) **conjugate** is removed from the **polymer** support and fully deprotected by treatment with ammonium hydroxide at room temperature for 1 hour followed by stirring at 55.degree.. . . .

DETD . . . sequence (SEQ. ID NO:1) synthesized on a 0.2 .mu.mole scale using the Peninsula Labs reagent is detritylated on an ABI **DNA** synthesizer using TCA. The top portion of the column is removed, and the CPG support is poured into a reaction. . . . support is filtered and washed three times with acetonitrile:water (8:1,v:v) followed by acetonitrile (3 times). The BGCA-ASAS (SEQ. ID NO:1) **conjugate** is removed from the **polymer** support and fully deprotected by treatment with ammonium hydroxide at room temperature for one hour, followed by stirring at 55.degree.. . . .

DETD The compounds of the invention have been shown to interact with, and permeabilize, biological **membranes** and to enhance the efficacy of antibiotics and antifungal agents in living cells. Since the compounds of the invention have been shown to permeabilize **membranes**, and the compounds themselves have no effect on cell growth at the concentrations used, it is presumed that the enhanced. . . .

DETD The utility of the compounds for permeabilizing **membranes** was demonstrated using an assay (Hoyt, D. W., et al. Biochemistry (1991) 30:10155) in which a fluorescein derivative is encapsulated. . . . upon addition of a test compound indicates leakage of the fluorescein derivative out of the vesicle and therefore implies a **disruption** or perturbation of the **membrane**. The compounds of the present invention induced a rapid and significant increase in fluorescent intensity at very low concentrations (0.05 mM-0.5 mM), indicating phospholipid **membrane** permeabilization.

DETD . . . not show significant changes in morphology relative to untreated vesicles. The glycosylated steroid derivatives of the present invention, therefore, permeabilize **membranes** without destroying the vesicles or inducing extensive fusion.

DETD . . . aggregates in solution and also on crystallographic evidence, that the glycosylated steroids of the present invention self-associate and insert into **membranes** in an associated form, and that **membrane** permeabilization is related to this process. Although the pure phospholipid vesicles used in this assay do not have the complexity of biological **membranes**, the inventors have shown that compounds which work well in this assay also enhance the action of therapeutically-significant-compounds (e.g., antibacterial. . . . indicates that the carboxyfluorescein assay is a reasonable initial model system for identifying potential candidates for the

permeabilization of biological **membranes**.

DETD . . . V. E. et al. J. Am. Chem. Soc. (1989) Vol. 111(2):767-769) was employed to determine whether the compounds make the **membranes** permeable to protons at extremely low concentrations (0.01 mM-0.005 mM). For this assay, the fluorescein derivative was encapsulated inside vesicles. . . 5.5. A compound of Formula (I) was then added at a concentration lower than the concentration required to make the **membranes** permeable to the fluorescein derivative. After addition of compounds of the Formula (I), the fluorescent intensity within the vesicles decreased,. . .

DETD The utility of the glycosylated steroid derivatives of the invention for permeabilizing phospholipid **membranes** suggested the usefulness of the derivatives for enhancing the permeability of cell **membranes**, which are composed in large part of phospholipids and other lipids, to therapeutically-significant-molecules. This use was demonstrated in assays testing. . .

DETD . . . that methanol alone does not cause a significant increase in fluorescent intensity. However, several of the glycosteroids efficiently permeabilized vesicle **membranes** at very low concentrations, permitting the carboxyfluorescein to leak out into the buffer. The results are summarized in Table II.

DETD . . . a measure of efficacy, then compounds 7, 8, and 11, are the most effective glycosylated steroids tested for permeabilizing phospholipid **membranes** in this assay. (The numbers of the compounds listed in Table II and III correspond to the compound entries of. . . attached to the hydrophilic face of the molecule. Cholic acid, deoxycholic acid, and chenodeoxycholic acid, compounds known to permeabilize biological **membranes** in other uses (Gordon G. S. et al. Proc. Nat'l. Acad. Sci. USA (1985) 82:7419-7423) also permeabilize **membranes** in this assay, although at much higher concentrations than many of the compounds of the present invention. From these observations, it may be concluded that glycosylation changes the chemical properties of the steroids, making them more efficient at permeabilizing **membranes**.

DETD Proton Transport across Lipid **Membranes**

DETD This assay was used to judge the ability of protons to pass across vesicle **membranes** treated with glycosteroids. Vesicles loaded with carboxyfluorescein at non-self-quenching concentrations were prepared exactly as described above except that the carboxyfluorescein. . .

DETD . . . 10 minutes. A significant decrease in fluorescence indicates that the glycosteroid in question facilitates the transport of protons across the **membrane**. This assay is based on the fact that the fluorescent intensity of carboxyfluorescein is much greater at pH 6.5 than. . . diluted into a buffer at pH 5.5, the fluorescent intensity will drop over time as the pH gradient across the **membrane** collapses.

DETD Erythromycin is an antibiotic whose efficacy is known to be increased by compounds that permeabilize cell **membranes** (Kubesch P. et al. Biochemistry (1987) 26:2139-2149). The efficacy of erythromycin, in the presence of novel glycosylated steroid derivatives of. . . to be more effective than chenodeoxycholic acid salts and cholic acid salts in enhancing the uptake of insulin through nasal **membranes** (Gordon G. S. et al. Proc. Nat'l. Acad. Sci. USA (1985) 82:7419-7423).

DETD . . . I described above (compound 8 in the carboxyfluorescein assay) and in Assays II and III described above, as a good **membrane** permeabilizing agent, was tested for its ability to enhance the efficacy of two different antifungal agents on the protozoan Crithidia. . .

CLM What is claimed is:

. . . (in which any oxygens which are not to be glycosylated have been protected by standard methods) in the presence of 2,6-di-tert-butyl-4-**methylpyridine** in toluene, for formation of .alpha.,.alpha. glycoside linkages, or in propionitrile, for the formation of .beta.,.beta. linkages which is then. . .

=> d bib abs 173 30

L73 ANSWER 30 OF 57 USPATFULL
AN 1998:33788 USPATFULL
TI **Complexes** of **nucleic acid** and **polymer**, their process of preparation and their use for the **transfection** of cells
IN Midoux, Patrick, Orleans, France
Erbacher, Patrick, Orleans, France
Roche-Degremont, Annie-Claude, Sandillon, France
Monsigny, Michel, Saint-Cyr-En-Val, France
PA I.D.M. Immuno-Designed Molecules, France (non-U.S. corporation)
PI US 5733762 19980331
AI US 1996-741678 19961031 (8)
RLI Continuation-in-part of Ser. No. US 1995-505068, filed on 21 Jul 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-288681, filed on 10 Aug 1994, now patented, Pat. No. US 5595897, issued on 21 Jan 1997
PRAI FR 1994-5174 19940428
DT Utility
EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Larson, Thomas G.
LREP Bierman, Muserlian and Lucas
CLMN Number of Claims: 15
ECL Exemplary Claim: 1,9,15
DRWN 34 Drawing Figure(s); 28 Drawing Page(s)
LN.CNT 2545
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound consisting essentially of polylysine conjugated to non-charged residues and recognition signals wherein the **free amino** functions of said polylysine are substituted with non-charged residues and said recognition signals, which non-charged residues consist of gluconalactone and which recognition signals are at least one member of the group consisting of galactoside, mannoside, fucoside, Lewis.sup.x, Lewis.sup.b, oligomannoside, oligolactosamine saccharides and peptide ANP and said conjugated polylysine contains at least 30% unsubstituted **free amino** functions and a method of **transfecting** cultured cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 30

L73 ANSWER 30 OF 57 USPATFULL
TI **Complexes** of **nucleic acid** and **polymer**, their process of preparation and their use for the **transfection** of cells
AB A compound consisting essentially of polylysine conjugated to non-charged residues and recognition signals wherein the **free amino** functions of said polylysine are substituted with non-charged residues and said recognition signals, which non-charged residues consist of gluconalactone and. . . galactoside, mannoside, fucoside, Lewis.sup.x, Lewis.sup.b, oligomannoside, oligolactosamine saccharides and peptide ANP and said conjugated polylysine contains at least 30% unsubstituted **free amino** functions and a method of **transfecting** cultured cells.
SUMM . . . either of modified virus material starting with vaccinia virus or retrovirus, or of targeted liposomes, or of targeted macromolecule gene **complexes**. **DNA**/carrier **complexes** such as **polylysine** substituted with asialoorosomucoide, insulin or transferrin have been proposed as targeted carriers of **plasmid** allowing cell **transfection** upon an endocytotic process induced by the corresponding receptors: the galactose specific receptor (lectin) with the asialoorosomucoide, the insulin receptor. . .
SUMM It has been **established** that numerous animal cells possess **membrane** lectins (Monsigny M., Roche A. C., Kieda C., Midoux P.,

Obrenovitch A. Characterization and biological implications of **membrane** lectins in tumor, lymphoid and myeloid cells. Biochemie, 1988: 70: 1633-49; Varki A. Selectin and other mammalian sialic acid binding. . . lectins. Curr. Op. in Cell. Biol., 1992, 4: 257-66] which specifically recognize the osides of various structures. In particular, the **membrane** lectin of cells of the hepatic parenchyma cells recognize oligosaccharides with a galactose residue in terminal non-reducing position, which means. . .

SUMM The specificity of these lectins depends on the cell type, and therefore **membrane** lectins are good candidates for gene transfer by glycoconjugate/DNA complexes as specific carriers. Soluble glycoconjugates bearing defined sugar moieties have. . .

SUMM Plasmid associated macromolecules capable of being specifically recognized by plasma **membrane** components of cell targets enter cells by a process mimicking the mechanism of entry of viral genetic material into cells. In every case described up to now, the macromolecular plasmid-carrier complex is specifically recognized by a **membrane** receptor which pulls the complex into intracellular vesicle endosomes by endocytosis, and probably into other deeper intracellular compartments, far from the plasma **membrane**. Moreover, the **transmembrane** passage of plasmid DNA is a critical process for its delivery into the cytosol and/or the nucleus, where the gene. . .

SUMM . . . invention to provide a compound consisting essentially of polylysine conjugated with non-charged residues in which at least 30% of the **free amino** functions ar unsubstituted.

SUMM It is another object of the invention to provide a novel method of **transfecting** cultured cells using the novel compounds in combination with a nucleic acid.

SUMM The invention is of new stable **complexes** of **nucleic acid** and of substituted **polymer**.

SUMM The invention also is of new **complexes** of **nucleic acid** and substituted **polymers** which are able, upon dissociation, to release **nucleic acid**, in order to allow an effective expression of **transfected nucleic acid** into the cells.

SUMM The invention is of new **nucleic acid complexes** and substituted **polymer** which do not contain any recognition signals and which are able to **transfect** several types of cells.

SUMM The invention is of new **nucleic acid complexes** and substituted **polymer** which contain recognition signals recognized by **membrane** receptors, making the **transfection** selective for different types of cells.

SUMM The invention is of a method of specific cell **transfection** in vitro or in vivo.

SUMM The invention also is of new **conjugates** of **polylysine** capable of being linked to a **nucleic acid** in preparation for the selective **transfection** of a cell.

SUMM The invention also includes a compound consisting essentially of polylysine conjugated to non-charged residues wherein the **free amino** functions of said polylysine are substituted with said non-charged residues, which non-charged residues are at least one member of the. . . galactoside, mannoside, fucoside, Lewis.sup.x, Lewis.sup.b, oligomannoside, oligolactosamine saccharides and peptide ANP and said conjugated polylysine contains at least 30% unsubstituted **free amino** functions.

SUMM The invention is also of new pharmaceutical compositions containing, as an active component, a **complex** of **DNA** and substituted **polymers**, particularly of substituted **polylysine**.

SUMM The invention is also of new **complexes** of **nucleic acid** and of substituted **polymer** possessing a high solubility in physiologic serum and divers culture mediums, capable of being administered in vivo at very high. . .

SUMM The invention, in one of its most general definitions, concerns a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate**, the association between the **nucleic acid** and the **polymeric conjugate** being

electrostatic in nature, the **polymeric conjugate** containing monomeric components harboring NH.sub.3.sup.+ free functions of the above-mentioned components, and being as follows:

SUMM . . . (NMR), by non-charged residues leading to a reduction of the number of positive charges in comparison with the same non-substituted **polymeric conjugate,** facilitating the release of **nucleic acid** by the dissociation of the **complex,**

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . aforementioned residues are also able to be substituted by a molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate, after substitution by the aforementioned residues and by the aforementioned recognition signals,. . .

SUMM i) the formation of stable **complexes** with a **nucleic acid, polynucleotides** RNA or **DNA,** particularly **DNA,** by electrostatic interactions between the negative charges of the **nucleic acid,** particularly **DNA,** and the remaining positive charges of the partially substituted **polymer** with the aforementioned resides, and

SUMM . . . complex and the release of the nucleic acid in order to allow an efficient expression of the gene in the **transfected** cells.

SUMM Furthermore, the presence of a cellular **membrane** recognition signal is not required.

SUMM The expression according to which "the residues substituting NH.sub.2 do not correspond to any cellular **membrane** recognition signal" means that they do not correspond to any signal according to what is known today in the literature.

SUMM By recognition signal recognized by a cellular **membrane** receptor, we generally mean a molecule or a molecular complex able to selectively recognize a ligand (signal-receptor affinity.gtoreq.10.sup.3 l/mole).

SUMM . . . acid (TNBS) (Fields R. (1971). The measurement of amino groups on proteins and peptides. Biochem. J., 124: 581-590) with the .epsilon.-**amino** groups of **free** lysine residues of the gluconoylated polylysine. The average number of gluconoyle residues bound per polylysine molecule was obtained from the. . .

SUMM The invention particularly concerns a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate,** the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components harboring free NH.sub.3.sup.+ functions of the aforementioned components, and being as follows:

SUMM . . . to 70%, particularly 60%, with non-charged residues leading to a reduction of positive charges in comparison with the same non-substituted **polymeric conjugate,** facilitating the release of the **nucleic acid** by dissociation from the **complex;**

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . are also able to be substituted with at least one molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM The invention particularly concerns a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate,** the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components harboring free NH.sub.3.sup.+ functions of the aforementioned components and being as follows:

SUMM . . . to 70%, particularly 60%, by non-charged residues leading to a reduction of positive charges in comparison with the same non-substituted **polymeric conjugate,** facilitating the release of the **nucleic acid** by dissociation from the **complex,**

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . residues are able to be substituted with at least one molecule which constitutes a recognition signal recognized by a cell **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM In accordance with an advantageous embodiment, the invention concerns a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate,** the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed from monomeric components which possess free NH.sub.3.sup.+ functions, in particular residues of lysine, and being as follows:

SUMM . . . particularly by approximately 60%, with non-charged residues leading to a reduction of positive charges in comparison with the same non-substituted **polymeric conjugate**, thus facilitating the dissociation of the **complex** and the release of the **nucleic acid,**

SUMM . . . functions of the above-mentioned components being also substituted by a molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, this recognition signal having a molecular mass less than 5,000, under the condition that the polymeric conjugate contains at. . .

SUMM The invention concerns more particularly a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate,** the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components which have free NH.sub.3.sup.+ functions, in particular residues of lysine and being as follows:

SUMM . . . particularly by approximately 60%, with non-charged residues leading to a reduction of positive charges in comparison with the same non-substituted **polymeric conjugate**, thus facilitating the dissociation of the **complex** and the release of the **nucleic acid,**

SUMM .fwdarw.they do not correspond to a cellular **membrane** recognition signal,

SUMM When they are present, the purpose of the recognition signals is to render selective the **transfection** with regards to the nature of different types of cells and to make the **transfection** effective in vivo.

SUMM . . . the R residues are able to be substituted by a molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM As demonstrated in the examples, HepG2 (human hepatocarcinoma) cells are efficiently **transfected** by the substituted polylysine containing 58.+-.12% (110.+-.22 residues) gluconoyle residues with an efficiency approximately 300 times higher than with the plasmid alone. The polylysines substituted by a few gluconoyle residues are not effective for obtaining a good **transfection;** those substituted by too many residues are slightly effective for obtaining a good **transfection.**

SUMM The polylysine substituted with 58.+-.12% gluconoyle residues has the ability to **transfect** different cells adhering or in suspension (from humans, mice, rats, rabbits, monkeys, etc.) with a great efficacy, modulated according to. . .

SUMM A) from simple or complex osides recognized by **membrane** lectins, and chosen among the following items:

SUMM CFTR cystic fibrosis **transmembrane** conductance regulator (mucoviscidose),

SUMM The invention also concerns a positively charged **polymeric conjugate,** the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components having free NH.sub.3.sup.+ functions of the aforementioned components and being

as follows:

SUMM . . . 70%, particularly by 60%, with non-charged residues leading to a reduction of positive charges in comparison with the same non-substituted **polymeric conjugate**, facilitating the release of **nucleic acid** by dissociation of the **complex**,

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . aforementioned residues may also be substituted with at least one molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM In accordance with an advantageous embodiment, the invention concerns a positively charged **polymeric conjugate**, the association between the **nucleic acid** the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components having free NH.sub.3.sup.+ functions and being as follows:

SUMM . . . 70%, particularly by 60%, with non-charged residues leading to a reduction of positive charges in comparison to the same non-substituted **polymeric conjugate**, facilitating the release of **nucleic acid** by dissociation of the **complex**,

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . aforementioned residues may also be substituted with at least one molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM In accordance with an advantageous embodiment, the invention concerns a **complex** between at least one negatively charged **nucleic acid** and at least one positively charged **polymeric conjugate**, the association between the **nucleic acid** and the **polymeric conjugate** being electrostatic in nature, the **polymeric conjugate** containing a **polymer** formed by monomeric components having free NH.sub.3.sup.+ functions of the aforementioned components and being as follows:

SUMM . . . 70%, particularly by 60%, by non-charged residues leading to a reduction of positive charges in comparison to the same non-substituted **polymeric conjugate**, facilitating the release of **nucleic acid** by dissociation of the **complex**,

SUMM .fwdarw.they do not correspond to a recognition signal recognized by a cellular **membrane** receptor,

SUMM . . . aforementioned residues may also be substituted by at least one molecule which constitutes a recognition signal recognized by a cellular **membrane** receptor, under the condition that the polymeric conjugate contains at least 30% free NH.sub.3.sup.+ functions.

SUMM the free NH.sub.3.sup.+ functions of the aforementioned components may also be substituted by a molecule which constitutes a cellular **membrane** recognition signal, this recognition signal having a molecular mass lower than 5,000 and when it is present, this recognition signal. . . .

SUMM In the polymeric conjugates of the invention, the cellular **membrane** recognition signal could be chosen from those which were clarified for the complexes described above.

SUMM In general terms, a polymer comprising primary **amines** (**free** NH.sub.3.sup.+ functions) is partially substituted by the reaction with an organic hydroxylated acid (in particular, gluconoic acid), in organic medium.

SUMM O-phenylisothiocyanate derivatives of monosaccharides reacted in DMSO in the presence of diisopropylethylamine with the .epsilon.-**amino** groups of the **free** lysine residues of partially gluconoylated polylysine as previously described in Midoux et al., 1993, Nucleic Acids Res., 21: 871-878.

SUMM . . . oligosaccharides were transformed into glycopeptides according to the method described by Nadia Normand Sdiqui, 1995, Synthesis of specific glycoconjugates of **membrane** lectins and their use for targeting oligonucleotides and genes. (University thesis, 5 Jan., 1995,

Orleans, France).
SUMM Phenylisothiocyanate of glycopeptide derivatives reacted with the .epsilon.-**amino** group of **free** lysine residues of the gluconoylated polylysine as previously described in: Midoux et al., 1993, Nucleic Acids Res., 21: 871-878.
SUMM The **nucleic acid/polymer conjugate complex** is obtained by mixing a solution of the **nucleic acid** and a solution of the **polymeric conjugate**. Preferably, the said solutions are prepared starting from physiologic serum and from a swab "(tampon") or from a cytocompatible medium.
SUMM The invention also concerns the use of a complex or of a conjugate according to the invention for the **transfection** in vitro, ex vivo or in vivo of cells with a gene, particularly those previously defined.
SUMM The invention also refers to the use of a complex or a conjugate according to the invention for the **transfection** of cells which may be chosen from the following:
SUMM A method of in vitro, ex vivo or in vivo **transfection** in the invention includes the introduction of a complex of the invention into a medium containing cells to be **transfected**, under conditions such that there exists:
SUMM transcription and expression of the nucleic acid into the **transfected** cells.
SUMM reagents permitting the **transfection** of the cell by the aforementioned complex.
SUMM The polymeric conjugates and the complexes of the invention are suitable to be used to **transfect** ex vivo all cells suited for antigen presentation, for example, precursors of macrophages, macrophages, B cells or dendritic cells.
SUMM When one wishes to **transfect** macrophages, they can be prepared according to the method described by M. Chokri et al. in Anticancer Research 12, 2257-2260,. . .
SUMM The complexes and polymeric conjugates of the invention are suitable to be used for the **transfection** of macrophages outside of the organism, while in culture environment, before or after separation by elutriation.
SUMM One can use a method analogous to that used for the **transfection** of HepG2 cells, but by using an appropriate oligosaccharide, for example mannose for the mannose receptor (for the **transfection** of HepG2 cells, one can refer to the examples which follow or to the article by C. Sureau, J. L. Romet-Lemonne, J. Mullins and M. Essex: "Production of hepatitis B virus by a differentiated human hepatoma cell line after **transfection** with cloned circular HBV DNA." Cell 47, p. 37-47, 1986, or the article by Midoux et al., entitled "Specific gene. . .
SUMM The macrophages **transfected** "ex vivo" are reinjected into the patient after the verification of the efficacy of the **transfection** according to the classic methods of immunolabeling.
SUMM In the case of vaccination by reinjection of **transfected** macrophages or other antigen presenting cells, the antigenic protein is expressed and is in part presented on the surface of. . .
SUMM for example:--**transfection** of the gene of g interferon; in this case the macrophage is permanently auto-activated, thus augmenting its cytotoxic properties;
SUMM **transfection** of a modified or unmodified TNFa gene; in this case there is an augmentation of the macrophages' anti-tumoral capacities;
SUMM for example: **transfection** of the IL2 gene for the stimulation of the cytotoxic T cells in the vicinity of the tumor colonized by. . .
DRWD Electrophoresis analysis of **plasmid** pSV2Luc **complexed** with gluconoylated **polylysine**.
DRWD The **DNA**/gluconoylated **polylysine complexes** were prepared by adding drop-wise under constant mixing, various quantities (from 0 to 8 .mu.g) of gluconoylated **polylysine** in 60 .mu.l of DMEM, to 2 .mu.g (0.6 pmol) of **plasmid** pSV2Luc in 140 .mu.l of DMEM. After 30 minutes at 20.degree. C., 20 .mu.l of each sample was analyzed by electrophoresis through 0.6% agarose gel containing ethidium bromide for visualizing the **DNA** in Tris borate EDTA buffer (95 mM Tris, 89 mM boric acid, and 2.5 mM EDTA), pH

8.6. pLK-GlcA/**DNA** ratios: 0 (a), 15 (b), 30 (c), 60 (d), 90(e), 120 (f), 150 (g), 180 (h), 210 (i) and 240. . . .

DRWD The **DNA/polymer complexes** formed between the pSV2Luc **plasmid** and the **polylysine** substituted by different quantities of gluconoyle residues (from 15 to 70%) have been determined by electrophoresis in agarose gel. The **polylysine** substituted by more than 140 gluconoyle residues is not able to form a **complex** with a **plasmid** stable enough.

DRWD . . . were incubated at 37.degree. C. for 4 hours in the presence of 100 .mu.M of chloroquine with 1.5 nM of **plasmid complexed** with each **conjugate**. The medium was discarded and the cells were further incubated in the absence of both chloroquine and **plasmid**. Expression of the gene of luciferase was determined 48 hours later by measuring the activity of luciferase in the cellular. . . 1.2 million of HepG2 cells, as a function and of the molar ratio GlcA/pLK and the degree of substitution of **polylysine** (%).

DRWD Formation of **DNA**/gluconoylated **polylysine complexes**. FIG. 2c concerns notably the study of the amount of gluconoylated **polylysine complexed** per **DNA** molecule (**plasmid** of 5 kb) as a function of the gluconoylated **polylysine/DNA** molar ratio (P/**DNA**). The **DNA**/gluconoylated **polylysine complexes** were formed in 1 ml of DMEM between the pSV2Luc **plasmid** (3 pmole) and gluconoylated **polylysine** labeled with fluorescein and containing 70 gluconoyle residues. The **complexes** were spun down from their solution by centrifugation at high speed. The amount of gluconoylated **polylysine** associated to a **DNA** molecule (white columns) is the total amount of gluconoylated **polylysine** (determined by measuring the absorbance at 495 nm of the solution before centrifugation: hatched column) minus the amount of the free gluconoylated **polylysine** (determined by measuring the absorbance at 495 nm of the supernatant after centrifugation: black column).

DRWD Formation of **DNA**/gluconoylated **polylysine complexes** as a function of the number of gluconoylated residues bound per **polylysine** molecule.

DRWD The **DNA**/gluconoylated **polylysine complexes** are formed in 0.2 ml of DMEM between the pSV2Luc **plasmid** (0.6 pmole) and gluconoylated **polylysines** containing up to 110 gluconoyle residues. The NH.sub.3.sup.+ /nucleotide ratio represents the number of positive charges per gluconoylated **polylysine** multiplied by the number of gluconoylated **polylysine** per **DNA** divided by the number of negative charges carried by the **DNA** into **complexes** with the smallest gluconoylated **polylysine/DNA** molar ratio inducing a complete retardation of all the **DNA** in electrophoresis. Insert: Variation of the amount of gluconoylated **polylysine** per **DNA** molecule in **complexes** with the smallest gluconoylated **polylysine/DNA** molar ratio inducing a complete retardation of all the **DNA** in electrophoresis. P/ **DNA** is the gluconoylated **polylysine DNA** molar ratio; GlcA/pLK is the average number of gluconoyle residues per **polylysine** molecule.

DRWD The **DNA/polymer complexes** formed between the pSV2Luc **plasmid** and the **polylysine** substituted by different quantities of gluconoyle residues (from 15 to 70%) were determined by electrophoresis on agarose gel. The **polylysine** substituted by more than 140 gluconoyle residues is not able to form a **complex** with the **plasmid** stable enough. The HepG2 cells were incubated at 37.degree. C. for 4 hours in presence of 100 .mu.M of chloroquine with 1.5 nM of **plasmid complexed** with each **conjugate**. The medium was discarded and the cells were incubated in the absence of both chloroquine and **plasmid**. Expression of the gene of luciferase was determined 48 hours later by measuring the activity of luciferase in the cellular. . . lysates. The relative light units (RLU) emitted were expressed in relation to those obtained in the same experiment where the **transfection** of HepG2 cells was with the lactosylated **polylysine**

conjugate (Lact.sub.60p pLK). In graph form, we represented the RLU/RLU values of the Lact.sub.60 pLK as a function of the molar ratio GlcA/pLK in one part, and by degree of substitution by **polylysine** (%).

DRWD A **DNA/polymer complex** was formed between the pSV2Luc **plasmid** and the **polylysine** substituted by 120 gluconoyle residues. The cells were incubated at 37.degree. C. for 4 hours in the presence of 100 .mu.M of chloroquine with 1.5 nM of **plasmid complexed** with the gluconoylated **polylysine**.

DRWD A **DNA/polymer complex** was formed between the CMVLuc **plasmid** and the **polylysine** substituted by 120 gluconoyle residues. The cells were incubated at 37.degree. C. for 4 hours in the presence of 100 .mu.M of chloroquine with 1.5 nM of **plasmid complexed** with gluconoylated **polylysine**. The medium was discarded and the cells were incubated in the absence of both chloroquine and **plasmid**. Expression of the gene of luciferase was determined 48 hours later by measuring the activity of luciferase in the cellular. . . .

DRWD The figure concerns the measure of the dissociation of the **complexes** formed between the pSV2Luc **plasmid** and the **polylysine** (degree of **polymerization**=190) substituted with lactose.

DRWD **Complexes** were formed between the pSV2Luc **plasmid** with either the **polylysine** (pLK), the **polylysine** substituted by 60 residues of lactose (Lact.sub.60 pLK), or **polylysine** substituted by 80 residues of lactose (Lact.sub.80 pLK). The **complexes** were formed in a solution of 0.15M NaCl; the concentration of NaCl was then increased. The solutions of **DNA/polymer complexes** at different concentrations in NaCl were filtered through a 0.45 mm nitrocellulose **membrane**. In this experiment, the **DNA** non-**complexed** to the **polylysine** passes through the filter while the **complexed DNA** is retained by the filter. The quantity of **DNA** dissociated from the **polylysine** was determined by measuring the quantity of **DNA** present in the filtrates using DAPI (4',5-diamino-2-phenylindole), (lem=450 nm; lexc=360 nm) (Sigma)) as fluorescent probe. We graphed the percentage of bound **DNA**/free **DNA** ratio as a function of the concentration of NaCl (M). .largecircle. corresponds to pLK, .circle-solid. corresponds to pLK,-Lact.sub.60, and .gradient.. . . .

DRWD **Complexes** of **DNA/polymer** were formed in a solution of 0.15M NaCl between pSV2Luc **plasmid** with either the **polylysine** (pLK), the gluconoylated **polylysine** (GlcA.sub.120 pLK), or with **polylysine** substituted by 60 residues of lactose (Lact.sub.60 pLK). After 30 minutes at 20.degree. C., the absorbency at 610 nm of. . . .

DRWD **DNA/polymer complexes** were formed in 0.15M NaCl between the pSV2Luc **plasmid** and the **polylysine** substituted with either 30 lactosyle residues (pLK, -Lact.sub.30) (empty squares), or 30 lactosyle residues and 50 gluconoyle residues (pLK, -Lact.sub.30,. . . .

DRWD HEL myeloid cells were **transfected** by a **complex** made between a **plasmid** containing the luciferase gene (PUT650) and the gluconoylated and biotinylated **polylysine**. This **complex** is then associated with the biotinylated Stem Cell Factor (SCF) by the intermediary of streptavidin. The RLU histogram values were expressed in relative units of luminescence per mg of protein extracts. The **transfections** were realized with (A) the **plasmid** alone, (B) the **plasmid complexed** to the gluconoylated and biotinylated **polylysine**, (C) the **complex** (**plasmid**/gluconoylated biotinylated **polylysine**) associated with the streptavidin and (D) the **complex** (**plasmid**/gluconoylated biotinylated **polylysine**) associated with the streptavidin and with the stem cell factor.

DRWD Human macrophages possess a mannose/fucose receptor and take up mannosylated or flucosylated macromolecules. As shown in FIG. 11, the **transfection** efficiency of human macrophages is 16 fold greater when partially gluconoylated polylysine is substituted with mannose

residues.

DRWD Human macrophages possess a mannose/fucose receptor and take up mannosylated or fucosylated macromolecules. As shown in FIG. 12, the **transfection** efficiency of human macrophages is 27 fold greater when partially gluconoylated polylysine is substituted with fucose residues.

DRWD . . . rabbit smooth muscle cell line, Rb-1 cells, possess a receptor for the peptide ANP. As shown in FIG. 13, the **transfection** efficiency of Rb-1 cells is 15 fold greater when partially gluconoylated polylysine is substituted with ANP residues.

DRWD FIGS. 16A-D is a flow cytometry analysis of the inhibition of the expression of the CAT marker protein by **transfection** with a plasmid encoding a specific antisense RNA. 3:1 and 3:2 negative controls. 3:3 positive control. 3:4 as in 3:3. . .

DRWD FIG. 17 shows the efficacy of **transfection** wherein the nucleus of cells expressing a large amount of galactosidase is blue

DRWD FIG. 18 shows the efficiency of the expression in stable **transfectants**

DRWD FIG. 19a corresponds to non **transfected** cells. FIG. 19b corresponds **transfected** cells, over expressing tat in their nucleus.

DRWD Confocal analysis of COS cells **transfected** with pc DNA.sub.3 MR 48 h after cell **transfection**, cells were fixed, permeabilized with saponin and incubated with fluoresceinylated mannosylated serum albumin. A high cytoplasmic fluorescence evidenced the over. . .

DETD Table 1. **Transfection** of HepG2 cells by lactolysated and gluconoylated polylysine.

DETD HepG2 cells were incubated at 37.degree. C. in the presence of 100 .mu.M of chloroquine and 1.5 nM of **plasmid complexed** with each of the **conjugates**. After 4 hours, the medium was discarded and the cells were incubated in the absence of both chloroquine and **plasmid**. Expression of the gene of luciferase was determined 48 hours later by measuring the activity of luciferase in the cellular. . . per mg of protein which corresponds to 1.2 million cells of HepG2. Lact/pLK is the number of lactose molecules per **polylysine** molecule, and GlcA/pLK is the number of gluconoyle molecules per **polylysine** molecule.

DETD Table II. **Transfection** of HepG2 cells by gluconoylated and biotinylated polylysine.

DETD HepG2 cells were incubated at 37.degree. C. in the presence of 100 .mu.M of chloroquine with 1.5 nM of free **plasmid** or **plasmid complexed** with each of the **conjugates**. After 4 hours, the medium was discarded and the cells were incubated in the absence of both chloroquine and **plasmid**. Expression of the gene of luciferase was determined 48 hours later by measuring the activity of luciferase in the cellular. . . The relative light units (RLU) emitted were expressed per mg of protein which corresponds to 1.2 million cells of HepG2. GlcA,Bio-pLK=**polylysine** substituted by 60 gluconoyles and 2.5 biotins; Strep=streptavidin; Bio-LactBSA=lactolysated and biotinylated albumin serum; Bio-BSA=biotinylated albumin serum.

DETD . . . USA); 4-isothiocyanatophenyl-b-D-lactoside, 4-isothiocyanatophenyl-b-D-galactopyranoside were prepared as previously described (Monsigny M., Roche A. C. and Midoux P., Uptake of neoglycoproteins via **membrane** lectins of L 1210 cells evidenced by quantitative flow cytofluorometry and drug targeting. Biol. Cell., 1984: 51: 187-96); the poly-L-lysine,. . . carcinoma cells. J. Cell. Biochem., 1983: 22: 131-40; Monsigny M., Roche A. C., and Midoux P., Uptake of neoglycoproteins via **membrane** lectin(s) of L 1210 cells evidenced by quantitative flow cytofluorometry and drug targeting. Biol. Cell., 1984: 51: 187-96).

DETD The **polylysines** substituted with either 30 lactose residues (Lact.sub.30 pLK) or with 60 lactose residues (Lact.sub.60 pLK) were prepared as previously described. . . Raimond J., Mayer R., Monsigny M., and Roche A. C. Specific gene transfer mediated by lactosylated poly-L-lysine into hepatoma cells. **Nucleic Acids** Res., 1993: 21: 871-78). The lactolysated **polylysine** containing 30 lactose residues (50 mg: 0.745 mmol) is allowed to react for 24 h at 20.degree. C. with the. . . mg; 43 mmol) in the presence

of diisopropylethylamine (24 ml; 200 mmol) and 1% of H.sub.2 O. The Lact.sub.30, -GlcA-pLK **polymer** is precipitated and purified as previously described. The mean number of bound gluconoyle residues per molecule of **conjugate** is determined by measuring the a-amino groups of the lysine which remains on the **polylysine** by using the TNBS colorimetric method (Fields R., The measurement of amino groups in proteins and peptides. Biochem. J., 1971:. . . .

DETD HepG2 cells (human hepatocarcinoma, ATCC 8065 HB) which possess a **membrane** lectin recognizing glycoproteins terminated with .beta.-D-galactose residues (Schwartz A. L., Fridovich S. E., Knowles B. B. and Lodish H. F.. . . . monocytes are prepared as described in Roche et al., 1985 (Roche A. C., Midoux P., Bouchard P. and Monsigny M. **Membrane** lectins on human monocytes: Maturation-dependent modulation of 6-phosphomannose and mannose receptors. FEBS Letters, 1985: 193: 63-68). 3LL cells are cultivated. . . .

DETD Formation of optimized **plasmid/polylysine conjugate complexes**

DETD Only the **complexes** for which no migration of **DNA** is produced in electrophoresis on agarose gel, thus named optimized **complexes** of **DNA/polymer,** are used for the **transfection** of cells. The molar ratios between the **polymer** and the **DNA** necessary for forming optimized pSV2Luc **plasmid/polymer complexes** are determined by electrophoresis on agarose gel at 0.6%: the **complexes** are prepared by adding, drop by drop under constant mixing, variable quantities of **polylysine conjugates** in 60 ml of DMEM, to 2 mg (0.6 pmol) of pSV2Luc **plasmid** in 140 ml of DMEM. After incubation for 30 minutes at 20.degree. C., 20 ml of each sample is analyzed by electrophoresis on 0.6% agarose gel (containing ethidium bromide for visualizing the **DNA**) in a Tris borate EDTA buffer (Tris 95 mM, boric acid 89 mM and EDTA 2.5 mM), pH 8.6.

DETD **Complexes** of pSV2Luc **plasmid** and **polylysine conjugates**

DETD Optimized **DNA/polymer complexes** are prepared by adding, drop by drop under constant agitation, the **polylysine** or a **conjugate** of poly-L-lysine (Lact.sub.60 pLK, GlcA.sub.x -PLK, 30<x<130, with Lact.sub.30 pLK, or Lact.sub.30 -GlcA.sub.30 -pLK) in 0.6 ml of DMEM at 20 mg (6 pmol) of pSV2Luc **plasmid** in 1.4 ml of DMEM. The solution is maintained for 30 minutes at 20.degree. C.

DETD The optimized **complexes** of pSV2Luc **plasmid** /biotinylated **polylysine** are formed by adding, drop by drop under constant mixing, 10 mg (172 pmol) of gluconoylated and biotinylated **polylysine** (containing 60 gluconoyle residues) in 290 ml of DMEM to 10 mg (3 pmol) of pSV2Luc **plasmid** in 0.7 ml of DMEM (molecular ratio between the **polymer** and the **DNA** close to 57:1). The solution is maintained for 30 minutes at 20.degree. C. The biotinylated neoglycoproteins (Lact-BSA and BSA) (377 pmol) in 0.5 ml of DMEM are then added, with constant stirring, to 1 ml of pSV2Luc **plasmid**/biotinylated **polylysine complex,** and then the streptavidin (27.5 mg; 490 pmol) in 0.5 ml of DMEM is added under agitation (molar ratio between the neoglycoprotein and the **DNA** close to 125:1) and the solution is maintained for 30 minutes at 20.degree. C.

DETD . . . on 12 well tissue culture plates, respectively. On day 1, after removing the medium, the solution (2 ml) containing the **plasmid /conjugate complex** of **polylysine** supplemented with 1% heat-inactivated bovine fetal serum, and with 100 .mu.M in the chloroquine (Luthman H. and Magnusson G. High efficiently polyoma **DNA transfection** of chloroquine treated cells. **Nucleic Acids** Res., 1983: 11: 1295-1308), is added to the wells. After 4 hours of incubation at 37.degree. C., the supernatant is. . . .

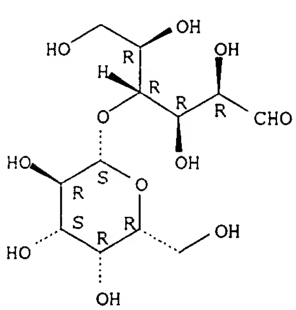
DETD The formation of **complexes** between a **plasmid** of 5 kb, such as the pSV2Luc **plasmid** containing the gene of luciferase with **polylysines** substituted with increasing quantities of gluconoyle residues, is analyzed by electrophoresis on agarose gel, and the optimized **DNA/polymer complexes** corresponding to those for which the **DNA**

does not migrate in electrophoresis following the total condensation of
<------User Break------>
u
=>

=> d bib abs hitstr l10 15

L10 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:666975 HCAPLUS
DN 123:48736
TI Glycosylated Polylysine/DNA **Complexes**: Gene Transfer Efficiency in Relation with the Size and the Sugar Substitution Level of Glycosylated Polylysines and with the Plasmid Size
AU Erbacher, Patrick; Roche, Annie Claude; **Monsigny, Michel**; **Midoux, Patrick**
CS Centre de Biophysique Moleculaire, CNRS, Orleans, F-45071, Fr.
SO Bioconjugate Chem. (1995), 6(4), 401-10
CODEN: BCCHES; ISSN: 1043-1802
DT Journal
LA English
AB A DNA delivery system based on the use of polylysine substituted with small recognition signals, such as carbohydrate moieties specifically recognized by membrane lectins present in a given cell line, has been developed [Midoux et al. (1993) Nucleic Acids Res. 21, 871-878]. Human hepatoma (HepG2) cells which express a galactose-specific membrane lectin are efficiently transfected in the presence of chloroquine with pSV2Luc plasmid **complexed** with a lactosylated polylysine. The optimization of the parameters involved in the formation of DNA/glycosylated polylysine **complexes** leads to the following conclusions: a high gene transfer efficiency is reached when (i) DNA/glycosylated polylysine **complexes** are completely retarded when subjected to electrophoresis and when (ii) 31 .+-. 4% or 40 .+-. 8% of the amino groups of a polylysine having a d.p. (DP) of 190 are substituted with lactosyl or .beta.-D-galactosyl residues, resp. In addn., carbohydrate residues bound to polylysine decrease the electrostatic strength between plasmid DNA and glycosylated polylysine, suggesting that the strength of the electrostatic interactions between the plasmid and the glycosylated polylysine plays an important role in the efficiency of the gene expression. The optimal lactosylated polylysine conjugate (polylysine DP 190 substituted with 60 lactosyl residues) transfers a 5 kb and a 12 kb plasmid with a similar efficiency.
IT **63-42-3**, Lactose **31258-47-6**, .beta.-D-Galactose
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(a high gene transfer efficiency is reached when (i) DNA/glycosylated polylysine **complexes** when 31 .+-. 4% or 40 .+-. 8% of the amino groups of a polylysine having a d.p. of 190 are substituted with lactosyl or .beta.-D-galactosyl residues, resp.)
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

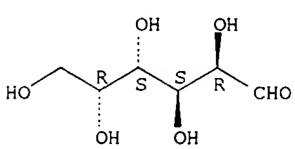


RN 31258-47-6 HCAPLUS
IT **25104-18-1**, Polylysine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(gene transfer efficiency of glycosylated polylysine/DNA

=> d bib abs hitstr l10 17

L10 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:206242 HCAPLUS
DN 118:206242
TI Specific gene transfer mediated by lactosylated poly-L-lysine into hepatoma cells
AU **Midoux, Patrick**; Mendes, Christina; Legrand, Alain; Raimond, Jacques; Mayer, Roger; **Monsigny, Michel**; Roche, Annie Claude
CS Cent. Biophys. Mol., CNRS, Orleans, F-45071, Fr.
SO Nucleic Acids Res. (1993), 21(4), 871-8
CODEN: NARHAD; ISSN: 0305-1048
DT Journal
LA English
AB Plasmid DNA/glycosylated polylysine **complexes** were used to transfer in vitro a luciferase reporter gene into human hepatoma cells by a receptor-mediated endocytosis process. HepG2 cells which express a galactose specific membrane lectin were efficiently and selectively transfected with pSV2Luc/lactosylated polylysine **complexes** in a sugar dependent manner: i) HepG2 cells which do not express membrane lectin specific for mannose were quite poorly transfected with pSV2Luc/mannosylated polylysine **complexes**, ii) HeLa cells which do not express membrane lectin specific for galactose were not transfected with pSV2Luc/lactosylated polylysine **complexes**. The transfection efficiency of HepG2 cells with pSV2Luc/lactosylated polylysine **complexes** was greatly enhanced either in the presence of chloroquine or in the presence of a fusogenic peptide. A 22-residue peptide derived from the influenza virus hemagglutinin HA2 N-terminal polypeptide that mimics the fusogenic activity of the virus, was selected. In the presence of the fusogenic peptide, the luciferase activity in HepG2 cells was 10 fold larger than that of cells transfected with pSV2Luc/lactosylated polylysine **complexes** in the presence of chloroquine.
IT **59-23-4**, Galactose, biological studies
RL: BIOL (Biological study)
(HepG2 cells contg. membrane lectin specific for, transformation of, with plasmid/glycosylated polylysine **complexes** by receptor-mediated endocytosis)
RN 59-23-4 HCAPLUS
CN D-Galactose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT **9014-00-0**, Luciferase
RL: BIOL (Biological study)
(gene for, transformation of HepG2 cells with, in plasmid/glycosylated polylysine **complexes**, by receptor-mediated endocytosis)
RN 9014-00-0 HCAPLUS
CN Luciferase (9CI) (CA INDEX NAME)

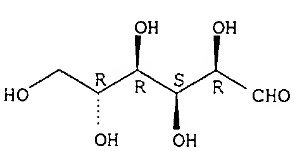
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **56-87-1**, Lysine, biological studies
RL: BIOL (Biological study)
(poly-, glycosylated, plasmid DNA **complexes** with, transformation of HepG2 cells with, by receptor-mediated endocytosis)
RN 56-87-1 HCAPLUS
CN L-Lysine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

=> d bib abs hitstr l10 10

L10 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:565516 HCAPLUS
DN 125:211681
TI Gluconoylated and glycosylated polylysines as vectors for gene transfer into cystic fibrosis airway epithelial cells
AU Kollen, Wouter J. W.; **Midoux, Patrick**; Erbacher, Patrick; Yip, Alex; Roche, Annie Claude; **Monsigny, Michel**; Glick, Mary Catherine; Scanlin, Thomas F.
CS School Medicine, University Pennsylvania, Philadelphia, PA, 19104, USA
SO Hum. Gene Ther. (1996), 7(13), 1577-1586
CODEN: HGTHE3; ISSN: 1043-0342
DT Journal
LA English
AB To provide an alternative to viral vectors for the transfer of genes into airway epithelial cells in cystic fibrosis (CF), a novel set of substituted polylysines were employed. Polylysine was partially neutralized by blocking a no. of pos. charged residues with gluconoyl groups. In addn., polylysine was substituted with sugar residues on a specified no. of amino groups. Using the gluconoylated polylysine as vector, the pCMVLuc plasmid gave high expression of the reporter gene luciferase in immortalized CF/T43 cells. The luciferase activity was 75-fold greater in the presence of 100 .mu.M chloroquine. Luciferase gene expression persisted at high levels for up to at least 120 h following transfection. Glycosylated polylysines/pCMVLuc **complexes** were compared to the gluconoylated polylysine/pCMVLuc **complex** and .beta.-Gal-, .alpha.-Glc-, and Lac-substituted polylysines gave 320%, 300%, and 290%, resp., higher expression of the reporter gene luciferase. Luciferase expression ranged from 35 to 2 ng of luciferase per mg of cell protein in the order: .beta.-Gal = .alpha.-Glc = Lac > .alpha.-Gal = Rha = Man > .beta.-GalNAc > .alpha.-GalNAc = .alpha.-Fuc, suggesting that the transfection efficiency is sugar dependent. Most importantly, in primary cultures of both CF and non-CF airway epithelial cells grown from tracheal tissue explants, lactosylated polylysine gave uniformly high expression of luciferase. The glycosylated polylysines provide an attractive nonviral approach for the transfer of genes into airway epithelial cells.
IT **50-99-7D**, Glucose, conjugated with polylysine **63-42-3D**, conjugated with polylysine **3458-28-4D**, Mannose, conjugated with polylysine **3615-41-6D**, Rhamnose, conjugated with polylysine **3646-73-9D**, .alpha.-D-Galactopyranose, conjugated with polylysine **7296-64-2D**, .beta.-D-Galactopyranose, conjugated with polylysine **14131-60-3D**, .beta.-N-**Acetylgalactosamine**, conjugated with polylysine **14215-68-0D**, .alpha.-N-**Acetylgalactosamine**, conjugated with polylysine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficiency of transformation of airway epithelium using; gluconoylated and glycosylated polylysines as vectors for gene transfer into cystic fibrosis airway epithelial cells)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



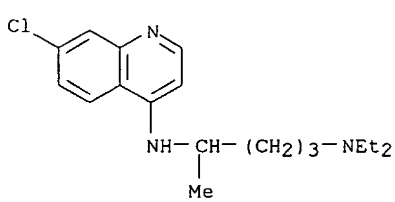
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

=> d bib abs hitstr l10 13

L10 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:283440 HCAPLUS
DN 125:26147
TI Gene transfer by DNA/glycosylated polylysine **complexes** into human blood monocyte-derived macrophages
AU Erbacher, Patrick; Bousser, Marie-Therese; Raimond, Jacques; **Monsigny, Michel; Midoux, Patrick;** Roche, Annie Claude
CS Centre de Biophysique Moleculaire, CNRS, Orleans, F-45071, Fr.
SO Hum. Gene Ther. (1996), 7(6), 721-729
CODEN: HGTHE3; ISSN: 1043-0342
DT Journal
LA English
AB Macrophages are putative target cells for expressing an exogenous gene with therapeutical effects. Knowing that macrophages express membrane lectins mediating endocytosis of their ligands, DNA/glycosylated polylysine **complexes** were used to transfect human blood monocyte-derived macrophages. Monocytes from human peripheral blood were matured in culture for 7 days to differentiate into macrophage-like cells in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF). Adherent cells, which displayed characteristic macrophage markers, CD 14, CD 11b, HLA-DR, and HLA-ABC antigens and mannose receptor, were transfected by DNA/glycosylated polylysine **complexes** in the presence of chloroquine. The luciferase reporter gene expression was maximal 24 h after transfection with a DNA/mannosylated polylysine **complex** and by using plasmids in which the promoters (either the long terminal repeat of the human immunodeficiency virus or the human cytomegalovirus) drove the luciferase gene expression. Luciferase gene expression was lower when the promoter was the early region of the large T antigen of SV40 virus. Transfection mediated by DNA/mannosylated polylysine **complexes** was much more efficient than with DEAE-dextran or lipofectin. The possibility of transferring and expressing an exogenous gene into macrophage-like cells by using a nonimmunogenic synthetic vector as a DNA carrier opens new ways to develop nonviral gene therapy strategies.
IT **9014-00-0,** Luciferase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene transfer by DNA/glycosylated polylysine **complexes** into human blood monocyte-derived macrophages)
RN 9014-00-0 HCAPLUS
CN Luciferase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **54-05-7,** Chloroquine
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(gene transfer by DNA/glycosylated polylysine **complexes** into human blood monocyte-derived macrophages)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)



IT **3458-28-4D,** Mannose, conjugates with polylysine **9015-73-0**
25104-18-1D, Polylysine, glycosylated **38000-06-5D,**

=> d bib abs l73 49

L73 ANSWER 49 OF 57 USPATFULL
AN 92:97225 USPATFULL
TI **Conjugates** of biologically stable **polymers** and **polynucleotides** for treating systemic lupus erythematosus
IN Conrad, Michael J., San Diego, CA, United States
Coutts, Stephen, Rancho Santa Fe, CA, United States
PA La Jolla Pharmaceutical Company, San Diego, CA, United States (U.S. corporation)
PI US 5162515 19921110
AI US 1990-494118 19900313 (7)
RLI Continuation-in-part of Ser. No. US 1990-466138, filed on 16 Jan 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Rollins, John W.
LREP Morrison & Foerster
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 788
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Chemically defined **conjugates** of biologically stable **polymers**, such as copolymers of D-glutamic acid and D-lysine, and **polynucleotide** duplexes of at least 30 base pairs that have significant binding activity for human lupus anti-dsDNA autoantibodies. The duplexes are preferably homogeneous in length and structure and are bound to the **polymer** via reaction between an amino-reactive functional group located at or proximate a terminus of each duplex. These **conjugates** are tolerogens for human systemic lupus erythematosus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 49

L73 ANSWER 49 OF 57 USPATFULL
TI **Conjugates** of biologically stable **polymers** and **polynucleotides** for treating systemic lupus erythematosus
AB Chemically defined **conjugates** of biologically stable **polymers**, such as copolymers of D-glutamic acid and D-lysine, and **polynucleotide** duplexes of at least 30 base pairs that have significant binding activity for human lupus anti-dsDNA autoantibodies. The duplexes are preferably homogeneous in length and structure and are bound to the **polymer** via reaction between an amino-reactive functional group located at or proximate a terminus of each duplex. These **conjugates** are tolerogens for human systemic lupus erythematosus.
SUMM . . . invention relates to compositions for treating the autoimmune disease systemic lupus erythematosus (SLE or "lupus"). More particularly it relates to **conjugates** of biologically stable **polymers**, preferably copolymers of D-glutamic acid (represented herein by the single letter designation "E") and D-lysine (represented herein by the single letter designation "K"), and certain **polynucleotides** that have been found to be effective for inducing tolerance to autoantigens involved in SLE. The preferred copolymers are represented. . .
SUMM . . . to glomerular nephritis. In these studies the treated animals produced significantly reduced levels of anti-denatured DNA antibodies and exhibited less **membranous** glomerulonephritis than control and free nucleoside-treated animals. In separate studies Parker et al. (J. Immunol. (1974) 113:292) evaluated the effect. . .
SUMM In contrast to the above described art applicants have developed chemically defined **conjugates** of biologically stable **polymers** and **polynucleotide** duplexes that are tolerogens for human SLE. These duplexes are defined with respect to

length, site of attachment to the **polymer**, helical structure, and binding affinity to human SLE anti-dsDNA autoantibodies. Accordingly, their chemistry and tolerogenic activity are reproducible to a degree that makes these **conjugates** amenable to quality control and approval as pharmaceuticals.

SUMM Thus, one aspect of the invention is a **conjugate** of a biologically stable **polymer** and a multiplicity of **polynucleotide** duplexes of at least about 30 base pairs each bound to the **polymer**, said duplexes each having a B-**DNA** type helical structure and significant binding activity for human SLE anti-dsDNA autoantibodies. In a preferred embodiment of these **conjugates**, the duplexes are substantially homogeneous in length and are coupled to the **polymer** at or proximate (i.e. within about 5 base pairs) one of their ends such that each duplex forms a pendant chain of B-**DNA** type helical structure of at least about 30 base pairs measured from the site of attachment of the duplex to the **polymer** to the free end of the chain.

SUMM Still another aspect is a **conjugate** of (a) a biologically stable **polymer** and (b) a multiplicity of **polynucleotide** duplexes each and all of which (i) is bound to the **polymer** by a functional group located at or proximate a terminus of one of the strands of the duplex and (ii) has a B-**DNA** type helical structure, said **conjugate** being a human SLE tolerogen.

SUMM A further aspect of the invention is a method for making the **conjugates** described above comprising: reacting a multiplicity of single-stranded **polynucleotides** each of which is at least about 30 nucleotides in length and has a functional group at or proximate one of its termini that reacts with **free amino** groups on the **polymer** to form a **conjugate** and annealing complementary single-stranded **polynucleotides** to the single-stranded **polynucleotides conjugated** to the **polymer** to form pendant chains of double-stranded **DNA** each of which has a B-**DNA** type helical structure.

DETD Preferably the **polynucleotide** duplexes of the invention **conjugates** are coupled or **conjugated** to the **polymer** at a site at or proximate one of their ends. Several **conjugation** strategies are available for so attaching the **oligonucleotides** to the biopolymer. The **polynucleotide** may be coupled to the **polymer** at the 3' end of the **polynucleotide** via a morpholino bridge formed by condensing an oxidized 3' terminal ribose on one of the strands of the **polynucleotide** with a **free amino** group on the **polymer** and then subjecting the adduct to reducing conditions to form the morpholino linkage. Such coupling requires the **polymer** to have at least an equal number of **free amino** groups (e.g., the epsilon amino groups of D-EK) to the number of **polynucleotide** duplexes to be bound to the **polymer**. The synthesis of such a **conjugate** is carried out in two steps. The first step is coupling one strand of the polyncleotide duplex to the **polymer** via the condensation/reduction reaction described above. The oxidized 3' terminal ribose is formed on the single **polynucleotide** strand by treating the strand with periodate to convert the 3' terminal ribose group to an oxidized ribose group. The single-stranded **polynucleotide** is then added slowly to an aqueous solution of the **polymer**

DETD of about pH 6.0 to 8.0 at 2-8.degree. C. The molar ratio of **polynucleotide** to **polymer** in all the **conjugation** strategies will normally be in the range of about 2:1 to about 30:1, preferably about 5:1 to 10:1. During or. . . sodium cyanoborohydride, is added to form the morpholino group. The complementary strand of the duplex is then added to the **conjugate** and the mixture is heated and slowly cooled to cause the strands to anneal. The **conjugate** may be purified by gel permeation chromatography.

DETD . . . with a molecular weight cutoff of 50,000 daltons. After extensive dialysis, the final conjugate is sterile-filtered through a 0.22 um **membrane**. It is characterized by uv spectroscopy, high

performance gel permeation liquid chromatography, polyacrylamide gel electrophoresis and thermography before sterile-filling.

DETD A trial of the **conjugate** was also carried out in older MRL mice, aged 22 to 24 weeks. Again, the mice were dosed i.p. once. . . . shown in FIG. 7. FIG. 7a shows the mean data from these tests. The variability in mice per dosage group (**conjugate**: 0.01, 0.1, 0.3 and 1.0 mg/mouse; control mice received a mixture of **polymer** carrier and unconjugated **nucleic acid** surrogate) reflects the deaths during the experiment.

CLM What is claimed is:

. . . 30 bases, said polynucleotide having a functional group at or proximate one of its termini that will react with a **free amino** group and which, when annealed to a complementary single-stranded polynucleotide, has a B-DNA type helical structure, and a significant binding. . . .

=> d bib abs hitstr l10 16

L10 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:427813 HCAPLUS
DN 123:413
TI Inhibition of human mammary cell line proliferation by membrane lectin-mediated uptake of Ha-ras antisense oligodeoxynucleotide
AU Sdiqui, Nadia; Arar, Khalil; **Midoux, Patrick**; Mayer, Roger; **Monsigny, Michel**; Roche, Annie-Claude
CS Biochimie des Glycoconjugues et Lectines Endogenes, Universite d'Orleans, Orleans, F-45071, Fr.
SO Drug Delivery (1995), 2(1), 63-72
CODEN: DDELEB; ISSN: 1071-7544
DT Journal
LA English
AB The Ha-ras oncogene promotes cell proliferation. Antisense oligonucleotides complementary to the ras gene sequence encompassing a mutated codon 12 selectively induce a cell proliferation inhibition. However, the concn. required to reach an effective inhibition is high due to the low efficiency of the oligonucleotide crossing through cell membranes, leading to a low concn. in the cytosol and/or the nucleoplasm. In concn. in the cytosol and/or the nucleoplasm. In the present paper, we show that anti-ras oligonucleotides linked to a glycosylated carrier, serum albumin bearing mannose 6-phosphate residues, are more efficient than free oligonucleotides or oligonucleotides bound to an unglycosylated carrier at inhibiting proliferation of a human tumor mammary cell line expressing the mutated Ha-ras. Using fluorescein-labeled neoglycoproteins and fluorescein-labeled oligonucleotides bound to neoglycoproteins, flow cytometry and confocal microscopy revealed that (i) these tumor cells express a membrane lectin specific for mannose 6-phosphate-bearing protein, (ii) the membrane lectin actively mediates the uptake of macromols. substituted with mannose 6-phosphate, and (iii) the fluorescein-labeled oligonucleotides bound to the neoglycoprotein accumulate in intracellular vesicles. Furthermore, with antisense oligonucleotides carried by the neoglycoproteins, the concn. required to inhibit cell proliferation is lower than that of the carrier-free antisense oligonucleotides.
IT **155663-54-0P 155663-55-1P 163755-21-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(in prepn. of Ha-ras antisense oligodeoxynucleotides conjugates with serum albumins bearing mannose phosphate residues and uptake by human mammary tumor)
RN 155663-54-0 HCAPLUS
CN DNA, d(A-C-A-C-C-G-A-C-G-G-C-[3'-O-[2-[2-[2-(2-pyridinyldithio)ethoxy]ethoxy]ethyl]]G), 5'-[[6-[[[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5-yl)amino]thioxomethyl]amino]hexyl]carbamate] (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 155663-55-1 HCAPLUS
CN DNA, d(A-C-A-C-C-G-A-C-G-G-C-[3'-[2-[2-(2-mercaptoethoxy)ethoxy]ethyl]]G), 5'-[[6-[[[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5-yl)amino]thioxomethyl]amino]hexyl]carbamate] (9CI) (CA INDEX NAME)

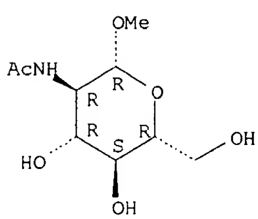
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 163755-21-3 HCAPLUS
CN DNA, d(A-C-A-C-C-G-A-C-G-G-C-[3'-O-(18-hydroxy-3,6,13,16-tetraoxa-9,10-dithiaoctadec-1-yl)]G), 5'-[(6-aminohexyl)carbamate] (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d bib abs hitstr l10 18

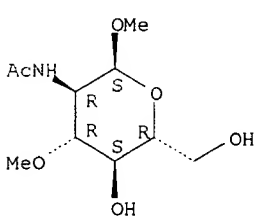
L10 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:172945 HCAPLUS
DN 100:172945
TI The binding of monosaccharides to wheat germ agglutinin: fluorescence and NMR investigations
AU **Midoux, P.**; Grivet, J. P.; Delmotte, F.; **Monsigny, M.**
CS Cent. Biophys. Mol., CNRS, Orleans, 45045, Fr.
SO Biochem. Biophys. Res. Commun. (1984), 119(2), 603-11
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB The interaction of N-acetyl- and N-trifluoroacetyl-glucosaminides with wheat germ agglutinin, a plant lectin specific for N-acetyl-**glucosamine** and sialic acid, was investigated by 1H and 19F NMR and fluorescence spectroscopy. Fluorescence spectroscopy relies on the existence of a competitive equil. involving the protein, the ligand, and O-(methylumbelliferyl)-N-acetyl-glucosaminide, a fluorescent saccharide. The binding consts. and the chem. shifts in the **complex** were detd. and were related to the protein structure.
IT **3946-01-8 10427-79-9 40299-07-8**
40299-08-9 40614-71-9
RL: BIOL (Biological study)
(binding of, to wheat germ agglutinin, fluorescence spectroscopy and NMR in study of)
RN 3946-01-8 HCAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 10427-79-9 HCAPLUS
CN .alpha.-D-Glucopyranoside, methyl 2-(acetylamino)-2-deoxy-3-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 40299-07-8 HCAPLUS
CN .alpha.-D-Glucopyranoside, methyl 2-deoxy-2-[(trifluoroacetyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

=> d bib abs l11 1

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:659307 HCAPLUS
TI Glycofectins: Synthetic vectors for a sugar specific gene targeting
AU **Midoux, Patrick; Monsigny, Michel**
CS Glycobiologie, Centre de Biophysique Moleculaire, CNRS, rue Charles Sadron, Orleans, 45071/2, Fr.
SO NATO Sci. Ser., Ser. A (2000), 323(Targeting of Drugs: Strategies for Gene Constructs and Delivery), 126-138
CODEN: NASAF2; ISSN: 1387-6686
PB IOS Press
DT Journal
LA English
AB Many cells express receptors (termed membrane lectins) that selectively recognize glycoconjugates contg. **complex** oligosaccharide structures. Membrane lectins mediate the uptake of their ligands into endosomes and then, glycoconjugates may be transferred to lysosomes. In addn., lectins are also present in intracellular compartments, in the cytosol and in the cell nucleus. Therefore, sugar residues can be used to achieve a specific gene delivery. We present recent progresses in i) the prepn. of glycofectins (glycosylated polylysines) suitable to form **complexes** (termed glycoplexes) with plasmid DNA and to transfect cells and ii) the synthesis of glycosynthons designed to easily link **complex** oligosaccharides on polylysine in order to prep. glycofectins with a very high binding capacity and selectivity towards cell surface lectins. Once taken up by cells, the transfer of a plasmid from intracellular acidic vesicles to the cytosol must occur before it can reach the cell nucleus for gene expression. We present strategies, based on the use of devices exhibiting membrane fusogenic or permeabilizing properties in acidic medium, suitable to destabilize vesicles contg. plasmids. They include the use of chloroquine, amphiphilic anionic peptides, peptides contg. several **histidines** and polylysine partially substituted with histidyl residues.
RE.CNT 56
RE
(2) Avrameas, A; Eur J Immunol 1996, V26, P394 HCAPLUS
(3) Boutin, V; Drug Delivery 1999, V6, P45 HCAPLUS
(4) Bowman, E; Proc Natl Acad Sci USA 1988, V85, P7972 HCAPLUS
(6) Dempsey, C; Biochim Biophys Acta 1990, V1031, P143 HCAPLUS
(7) Duverger, E; Glycobiology 1996, V6, P381 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind

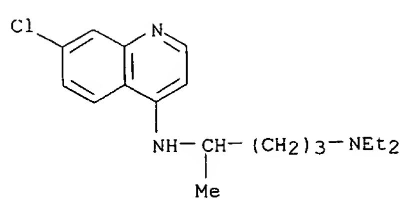
L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2000 ACS
CC 63 (Pharmaceuticals)

=> d bib abs l11 2

L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:929139 HCAPLUS
DN 124:66258
TI Sugar specific delivery of drugs, oligonucleotides and genes
AU **Monsigny, M.**; Roche, A.-C.; **Midoux, P.**; Mayer, R.
CS Laboratoire de Biochimie des Glycoconjugues et Lectines Endogenes, Universite d'Orleans, Orleans, 45071, Fr.
SO NATO ASI Ser., Ser. A (1994), Volume Date 1994, 273, 31-50
CODEN: NALSDJ; ISSN: 0258-1213
DT Journal; General Review
LA English
AB A review with many refs. Membrane lectins of various cell types actively take up glycoconjugates in a sugar specific. way. On these bases, many therapeutic drugs have been rendered cell specific. In addn. glycoconjugates have been shown to be suitable to transfer oligonucleotides and genes inside cells which express a membrane lectin able to recognize the sugar moiety used as recognition signal. Several improvements are expected: they include the use of **complex** oligosaccharides to reach a higher cell selectivity, the use of helper peptides allowing a larger efficiency in the transfer of hydrophilic drugs, of oligonucleotides, and of genes into the cytosol and into the nucleus.

=> d bib abs hitstr l10 9

L10 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:6461 HCAPLUS
DN 126:99920
TI Enhanced biological activity of antisense oligonucleotides **complexed** with glycosylated poly-L-lysine
AU Stewart, A. J.; Pichon, C.; Meunier, L.; **Midoux, P.**; **Monsigny, M.**; Roche, A. C.
CS Centre National Recherche Scientifique, Univ. Orleans, Orleans, 45071, Fr.
SO Mol. Pharmacol. (1996), 50(6), 1487-1494
CODEN: MOPMA3; ISSN: 0026-895X
PB Williams & Wilkins
DT Journal
LA English
AB We sought to exploit glycosylated poly-L-lysine (pLK) to increase the uptake and biol. antisense activity of a phosphorothioate oligonucleotide (pt-odn) [pt-odn complementary to the 3' noncoding region of intercellular adhesion mol.-1 (ICAM-1) (odnICAM-a1)] complementary to the 3'-noncoding region of ICAM-1 in A549 cells. Dose-dependent inhibition of ICAM-1 expression was obtained (IC50 = 500 nM) through treatment of cells with odnICAM-1 **complexes** with pLK carrying fucose residues in the presence of 100 .mu.M chloroquine. Alteration in the charge ratio between fucosylated pLK and pt-odn had a significant effect on the efficacy of inhibition (optimal conditions, charge ratio = 1.1). This effect was also dependent on the no. of fucose moieties per pLK. Free pt-odn or pt-odn **complexed** with nonglycosylated pLK gave no inhibition at concns. of .ltoreq.2 .mu.M. Two control pt-odn (one was targeted against an unrelated gene and not present in these cells, gagHIV, and the other had a randomized sequence) gave no inhibition of ICAM-1 expression in the presence or absence of pLK carrying fucose residues at concns. of .ltoreq.2 .mu.M. When **complexed** with pLK carrying 100 fucose residues, the amt. of cell-assocd. pt-odn was increased by 15-fold compared with the free pt-odn. Nonglycosylated pLK also increased the amt. of cell-assocd. pt-odn by >10 fold but did not alter the biol. activity. These results demonstrate clearly the potential of glycosylated pLK as a pt-odn transporter.
IT **54-05-7**, Chloroquine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(cellular uptake of antisense oligonucleotides **complexed** with glycosylated poly-L-lysine response to)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)



IT **25104-18-1D**, Poly-L-lysine, fucose derivs., **complexes** with antisense oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(enhanced biol. activity of antisense oligonucleotides **complexed** with glycosylated poly-L-lysine)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

STR SEARCH


```
=> d his

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L2          1 S 38000-06-5
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L4            STR
L5         50 S L4 SSS SAM SUB=L3
L6          2 S L3 AND (L1 OR L2)
L7      32848 S PM/PCT
L8      98919 S L7 OR L3
L9         50 S L4 SSS SAM SUB=L8
L10     23078 S L4 SSS FUL SUB=L8

     FILE 'HCAPLUS' ENTERED AT 15:50:53 ON 28 OCT 2000
L11     41489 S L10
L12    659530 S DNA OR OLIGONUCLEOTID? OR POLYNUCLEOTID? OR VECTOR OR PLASMID
L13       778 S L11(L)L12
L14   1219338 S COMPLEX? OR CONJUGAT?
L15        86 S L13(L)L14
L16    572281 S ?MEMBRAN?
L17     53064 S TRANSFECT?
L18         2 S L15 AND (L16 OR L17)
L19        25 S L13 AND (L16 OR L17)
L20     29191 S FREE(5A)(AMIN## OR LYS OR LYSIN# OR AMMON? OR "NH3+")
L21         1 S L20 AND L15
L22         4 S L20 AND L13
L23    221591 S ?QUINOLIN? OR ?IMIDAZOL? OR ?HISTIDIN? OR ?PTERIN?
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L25        22 S L24 AND L14
L26        25 S L24 NOT L25
L27         8 S L24 AND L16-17
L28        27 S L25 OR L21 OR L27 OR L25
L29        12 S L28 AND PY>1997
L30        15 S L28 NOT L29

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L33        19 S L32 AND L31
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L35           STR L31
L36        50 S L35
L37        19 S L32 AND L35
L38         0 S L35 SSS SAM SUB=L34
L39           SCREEN 2043 AND  1992
L40        17 S L35 AND L39
L41       415 S L35 AND L39 FUL
              SAVE L41 NGU519P/A

     FILE 'HCAPLUS' ENTERED AT 17:45:34 ON 28 OCT 2000
L42       555 S L41
L43         2 S L42 AND QUINOLIN?
L44        95 S L42 AND L12
L45        32 S L14 AND L44
L46        33 S L43 OR L45
L47        23 S L46 NOT L28
```

1ST STRATEGY: search very general str for rings against polyamides & polyamines

L3: all types of polyamides

L7: all types of polyames

joined these 2 groups to make the parent set

L10: 23078 cpds (polymers)

L11: 41,489 cites for L10

L29: priority date

L30: 15 cites

2nd STRATEGY – search for monomers

L39: screen: for polymers & cpd has at least 1 N

L41: 415 monomers

L42: 555 cites for L41

L47: 23 cites

=> d que l11

L3 70666 SEA FILE=REGISTRY ABB=ON PLU=ON PA/PCT — parent set
L4 STR

Hy 1 ← polymer must have a aryl heterocycle w/ at least 1 N

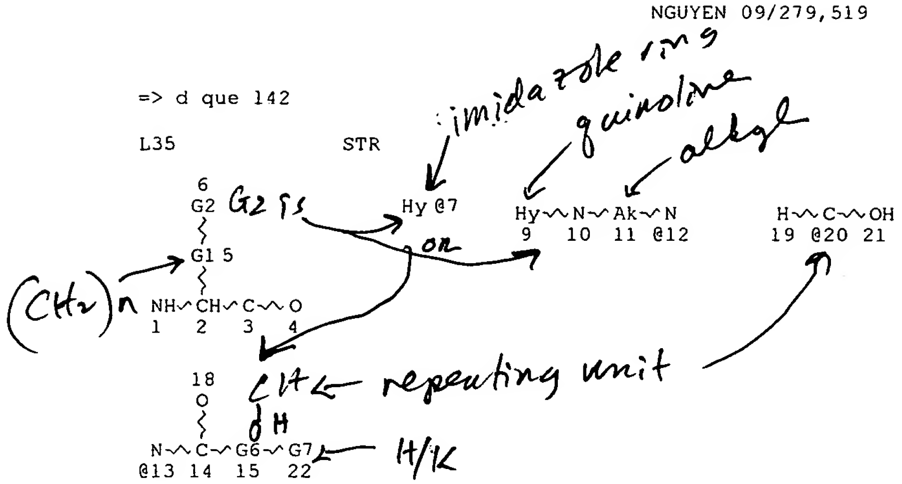
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 1
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M1 N AT 1

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 1

STEREO ATTRIBUTES: NONE
L7 32848 SEA FILE=REGISTRY ABB=ON PLU=ON PM/PCT
L8 98919 SEA FILE=REGISTRY ABB=ON PLU=ON L7 OR L3
L10 23078 SEA FILE=REGISTRY SUB=L8 SSS FUL L4
L11 41489 SEA FILE=HCAPLUS ABB=ON PLU=ON L10

=> d que 142

L35 STR



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REP G6=(1-10) 20-14 20-22
VAR G7=H/AK
NODE ATTRIBUTES:
CONNECT IS E2 RC AT 11
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 7
GGCAT IS PCY UNS AT 9
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E3 C E2 N AT 7
ECOUNT IS E9 C E1 N AT 9

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE

L39		SCR 2043 AND 1992
L41	415	SEA FILE=REGISTRY SSS FUL L35 AND L39
L42	555	SEA FILE=HCAPLUS ABB=ON PLU=ON L41

=> d bib abs hitstr l30 1

L30 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:622337 HCAPLUS
DN 127:287823
TI Characterizing the DNA binding modes of a topoisomerase I-poisoning **terbenzimidazole**: evidence for both intercalative and minor groove binding properties
AU Pilch, Daniel S.; Xu, Zhitao; Sun, Qun; Lavoie, Edmond J.; Liu, Leroy F.; Geacintov, Nicholas E.; Breslauer, Kenneth J.
CS Department of Chemistry, Rutgers-The State University of New Jersey, New Brunswick, NJ, 08903, USA
SO Drug Des. Discovery (1996), 13(3-4), 115-133
CODEN: DDDIEV; ISSN: 1055-9612
PB Harwood
DT Journal
LA English
AB We have used a broad range of spectroscopic and viscometric techniques to demonstrate that the **complexation** of a cytotoxic, topoisomerase I-poisoning **terbenzimidazole** (5PTB) with the poly(dA).cntdot.poly(dT) duplex exhibits properties characteristic of both intercalation and minor groove binding. Our results reveal the following features: (i) Optical melting profiles reveal that 5PTB binding enhances the thermal stability of the poly(dA).cntdot.poly(dT) duplex; (ii) Fluorescence-detected 5PTB binding to the poly(dA).cntdot.poly(dT) duplex reveals four apparent "site sizes," ranging from 1 to 13 base pairs (bp) per bound drug; (iii) Flow linear dichroism data suggest conformational heterogeneity among the poly(dA).cntdot.poly(dT)-bound 5PTB mols., with substantial contributions from drug mols. bound in the minor groove; (i.v.) Fluorescence resonance energy transfer data reveal properties characteristic of a significant contribution from an intercalative mode of binding; (v) Viscometric, fluorescence quenching, and netropsin competition data are consistent with 5PTB binding to poly(dA).cntdot.poly(dT) by "mixed" modes, which are operationally defined as single or multiple binding populations that individually and/or collectively express both intercalative and minor groove binding properties. We comment on a potential correlation between drugs that exhibit such "mixed" mode binding motifs and those that express antineoplastic activity through inhibition of topoisomerase I.
IT **24939-09-1**, Poly(dA).poly(dT)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**DNA** binding modes of a topoisomerase I-poisoning **terbenzimidazole**)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

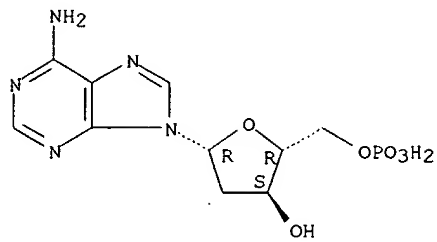
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



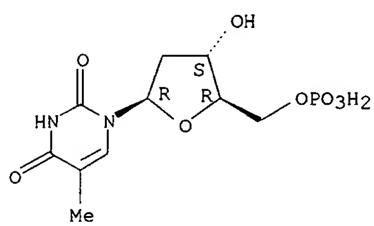
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

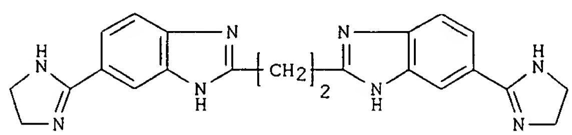
CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.



=> d bib abs hitstr l30 2

L30 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:148292 HCAPLUS
DN 124:249741
TI Synthesis and DNA interactions of **benzimidazole** dications which have activity against opportunistic infections
AU Lombardy, Richard L.; Tanious, Farial A.; Ramachandran, Kishore; Tidwell, Richard R.; Wilson, W. David
CS Department of Chemistry, Georgia State University, Atlanta, GA, 30303, USA
SO J. Med. Chem. (1996), 39(7), 1452-62
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 124:249741
GI



I

AB Considerable evidence now indicates that DNA is the receptor site for dicationic **benzimidazole** anti-opportunistic infections agents. To obtain addnl. information on **benzimidazole**-receptor **complexes**, the syntheses and DNA interactions of series of sym. **benzimidazole** cations, linked by alkyl or alkenyl groups, have been evaluated. Biophys. techniques, thermal denaturation measurement (.DELTA.Tm), kinetics, and CD have been used in conjunction with NMR and mol. modeling to evaluate the affinities, binding mode, and structure of **complexes** formed between these compds. and DNA. All of the compds. bind strongly to DNA samples with four or more consecutive AT base pairs, and they bind negligibly to GC rich DNA or to RNA. Spectral and kinetics characteristics of the **benzimidazole complexes** indicate that the compds. bind in the DNA minor groove at AT sequences. NMR and mol. modeling of the **complex** formed between an ethylene-linked **benzimidazole** deriv. I and the self-complementary oligomer d(GCGAATTCGC) have been used to establish structural details for the minor groove **complex**. These results have been used as a starting point for mol. mechanics calcns. to refine the model of the minor groove-**benzimidazole complex** and to draw conclusions regarding the mol. basis for the effects of substituent changes on **benzimidazole**-DNA affinities.
IT **24939-09-1,** Poly(dA).cntdot.poly(dT)
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process)
(synthesis and **DNA** interactions of **benzimidazole** dications in relation to anti-Pneumocystis carinii pneumonia agents)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

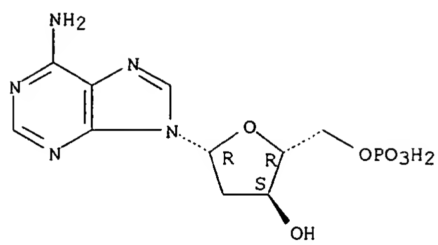
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



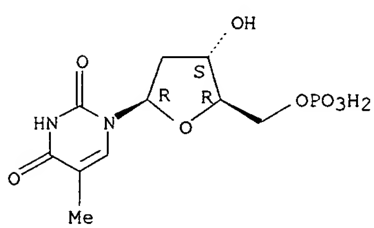
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.



=> d bib abs hitstr l30 3

L30 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:691473 HCAPLUS
DN 123:132012
TI Small changes in cationic substituents of diphenylfuran derivatives have major effects on the binding affinity and the binding mode with RNA helical duplexes
AU Zhao, Min; Ratmeyer, Lynda; Peloquin, Robert G.; Yao, Shijie; Kumar, Arvind; Spychala, Jaroslaw; Boykin, David W.; Wilson, W. David
CS Center Biotechnology and Drug Design, Georgia State University, Atlanta, GA, 30303, USA
SO Bioorg. Med. Chem. (1995), 3(6), 785-94
CODEN: BMECEP; ISSN: 0968-0896
DT Journal
LA English
AB The interactions of dicationic and tetracationic diphenylfuran analogs of the antimicrobial furamidine with RNA have been analyzed by thermal melting, spectroscopic, viscometric, kinetic and mol.-modeling techniques. The results of these studies indicate that most of the furan derivs. bind to RNA duplexes by intercalation in contrast to their minor-groove binding mode in AT sequences of DNA, but similar to their binding mode in GC rich regions of DNA. The highest affinity for RNA is found for an **imidazoline** dication. With some substituents which inhibit formation of a strong intercalation **complex,** the results suggest a non-intercalative type of binding occurs. The non-intercalative binding probably occurs through a **complex** with the furan deriv. bound in the narrow, deep major groove of A-form RNA helixes.
IT **24939-09-1,** PolydA-polydT
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(interaction of cationic diphenylfuran analogs of antimicrobial furamidine with RNA and **DNA**)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

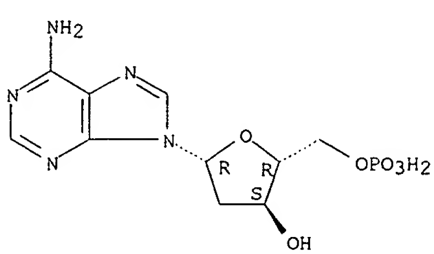
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



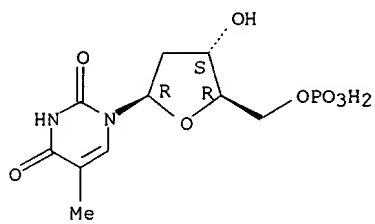
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

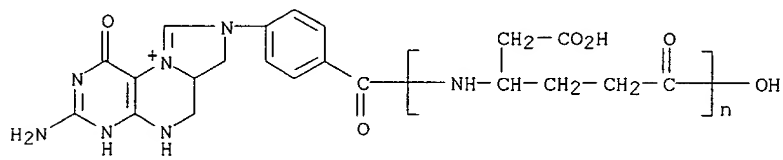
CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.



=> d bib abs hitstr 130 4

L30 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:443289 HCAPLUS
DN 117:43289
TI Reconstitution of apophotolyase with **pterin** and/or flavin derivatives
AU Jorns, M. S.; Wang, B.; Jordan, S. P.; Chanderkar, L. P.
CS Dep. Biol. Chem., Hahnemann Univ., Philadelphia, PA, 19102, USA
SO Flavins Flavoproteins Proc. Int. Symp., 10th (1991), Meeting Date 1990, 819-26. Editor(s): Curti, Bruno; Ronchi, Severino; Zanetti, Giuliana. Publisher: de Gruyter, Berlin, Fed. Rep. Ger.
CODEN: 57OEAQ
DT Conference
LA English
AB DNA photolyase repairs pyrimidine dimers in UV-damaged DNA in a rather unusual catalytic reaction which requires visible light. The active and physiol. significant form of the enzyme from Escherichia coli contains 1,5-dihydroFAD (FADH2) plus 5,10-methenyltetrahydropteroylpolyglutamate (5,10-CH+-H4Pte(glu)n). Either chromophore can act as a sensitizer in catalysis. The flavin chromophore in the isolated enzyme is present as an air-stable blue neutral FAD radical (FADH.bul.) but is readily converted to FADH2 with dithionite or photochem. Formation of an enzyme-substrate **complex** stabilizes FADH2 against air oxidn. and also quenches the chromophore fluorescence in a reaction that is fully reversible upon dimer repair. The isolated enzyme is depleted with respect to the **pterin** chromophore but can bind addnl. 5,10-CH+-H4Pte(Glu)n or 5,10-methenyltetrahydrofolate (5,10-CH+-H4folate) to yield enzyme contg. equimolar amts. of flavin and **pterin**. Redn. of the **pterin** chromophore with borohydride yields 5-methyltetrahydropterolypolyglutamate (5-CH3-H4Pte(Glu)n) in a reaction that is accompanied by a complete loss of the chromophore's visible absorption and fluorescence; enzyme activity is unaffected, suggesting that the **pterin** chromophore is not essential for catalysis. This chapter describes reconstitution expts. with apophotolyase which provide addnl. information regarding chromophore function.
IT **138874-28-9D**, derivs.
RL: BIOL (Biological study)
(**DNA** photolyase apo form reconstitution with)
RN 138874-28-9 HCAPLUS
CN Poly[imino[1-(carboxymethyl)-4-oxo-1,4-butanediyl]], .alpha.-[4-(3-amino-1,2,5,6,6a,7-hexahydro-1-oxo-8H-imidazo[1,5-f]pteridin-10-ium-8-yl)benzoyl]-.omega.-hydroxy- (9CI) (CA INDEX NAME)



=> d bib abs hitstr l30 5

L30 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:146716 HCAPLUS
DN 116:146716
TI A molecular model of the complete three-dimensional structure of the Klenow fragment of Escherichia coli DNA polymerase I: binding of the dNTP substrate and template-primer
AU Yadav, Prem N. S.; Yadav, Janardan S.; Modak, Mukund J.
CS New Jersey Med. Sch., Univ. Med. Dent. New Jersey, Newark, NJ, 07103, USA
SO Biochemistry (1992), 31(11), 2879-86
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB A complete 3-dimensional structure of the Klenow fragment of E. coli DNA polymerase I was proposed on the basis of mol. modeling and mol. mechanics studies. The structure appeared quite reliable because the overall surface of electrostatic potentials calcd. for the molecularly modeled enzyme closely resembled that reported for the x-ray structure. The modeled structure was then used in developing a ternary **complex** of dTTP and (dA)25-(dT)14 poised in its active site. The orientation of both substrates in the ternary **complex** was primarily guided by the amino acid residues which had been known to interact with dNTP and DNA substrates from earlier studies. The proposed model explains the geometric and physicochem. relations of the 2 substrates with the various crit. amino acid residues involved in the binding process and suggests possible roles for addnl. residues in the binding and/or polymn. reaction. Furthermore, the ternary **complex** appears to satisfy many biochem. and genetic data concerning catalytic requirements known to exist for the polymn. reaction.
IT **139493-16-6**
RL: BIOL (Biological study)
(**DNA** polymerase I Klenow fragment of Escherichia coli binding of, mol. modeling study of)
RN 139493-16-6 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-thymidine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 92767-30-1
CMF C140 H183 N28 O96 P13
CCI MAN
CDES 5:ALL,B-D-ERYTHRO

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

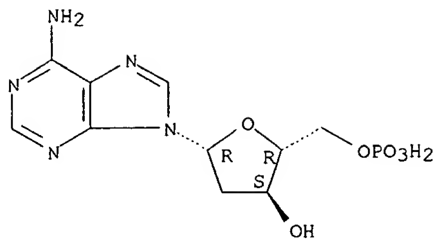
CM 2

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 3

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).


NH2
N
N
N
N
O
R
R
S
OPO3H2
OH

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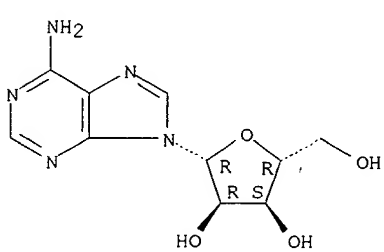
=> d bib abs hitstr l30 6

L30  ANSWER 6 OF 15  HCAPLUS  COPYRIGHT 2000 ACS
AN   1991:578207  HCAPLUS
DN   115:178207
TI   Immobilization of nucleic acids on solid surfaces for nucleic acid
     hybridization assays
IN   Bahl, Chander; Lang, Rhonda; Mendoza, Leo
PA   Ortho Diagnostic Systems, Inc., USA
SO   Can. Pat. Appl., 25 pp.
     CODEN: CPXXEB
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.   DATE
     ---------------  ----  --------      ---------------   --------
PI   CA 2031026        AA   19910531      CA 1990-2031026   19901128
     US 5215882        A    19930601      US 1989-444031    19891130
     EP 435470         A1   19910703      EP 1990-313007    19901129
     EP 435470         B1   19970115
         R:  AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE
     AT 147860         E    19970215      AT 1990-313007    19901129
PRAI US 1989-444031    19891130
AB   A method for immobilizing nucleic acids uses a modified nucleic acid
     having a variable portion and an anchor portion contg. a primary
     amine function, that reacts with free aldehyde groups of
     a solid surface in the presence of a reducing agent.  A
     hexanediamine-modified oligonucleotide was incubated with com. aldehyde
     paper, the paper was then treated with amino caproic acid and Na
     cyanoborohydride to complete the immobilization reaction.
IT   30143-02-3D, Polyadenosin, nucleic acid
     conjugates
     RL: PRP (Properties)
        (immobilization on aldehyde group-contg. solid surface of)
RN   30143-02-3  HCAPLUS
CN   Adenosine, homopolymer (9CI)  (CA INDEX NAME)

     CM   1

     CRN  58-61-7
     CMF  C10 H13 N5 O4

Absolute stereochemistry.
```



=> d bib abs hitstr l30 7

L30 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:185397 HCAPLUS
DN 110:185397
TI Mechanism of inhibition of DNA gyrase by quinolone antibacterials: specificity and cooperativity of drug binding to DNA
AU Shen, Linus L.; Baranowski, John; Pernet, Andre G.
CS Anti-Infect. Res. Div., Abbott Lab., Abbott Park, IL, 60064, USA
SO Biochemistry (1989), 28(9), 3879-85
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB Although the functional target of quinolone antibacterials such as nalidixic acid and norfloxacin has been identified as the enzyme DNA gyrase, the direct binding site of the drug is the DNA mol. (L. L. Shen and A. G. Pernet, 1985). The binding specificity and cooperativity of quinolones to DNA were further investigated with the use of a variety of DNA species of different structures and different base compns. Results show that the drug binding specificity is controlled and detd. largely by the DNA structure. The drug binds weakly and demonstrates no base preference when DNA strands are paired. The drug binds with much greater affinity when the strands are sepd., and consequently, binding preference emerges: it binds better to poly(G) and poly(dG) over their counterparts including poly(dI). The results suggest that the drug binds to unpaired bases via H-bonding and not via ring stacking with DNA bases. The weak binding to relaxed double-stranded DNA and the stronger binding to single-stranded DNA are both nonspecific as they do not demonstrate binding satn. and cooperativity. The specific type of binding, initially demonstrated with the supercoiled DNA and more recently with **complex** formed between linear DNA and DNA gyrase (L. L. Shen et al. in press) occurs near the drug's supercoiling inhibition concn. As shown in this paper, binding satn. curves of this type are highly cooperative (with Hill const. >4). This form of binding represents a specific mode of drug binding which dets. the drug's biol. potency.
IT **24939-09-1**, Poly(dA).cntdot.poly(dT)
RL: BIOL (Biological study)
(quinolone antibacterials binding to, **DNA** gyrase inhibition mechanism in)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

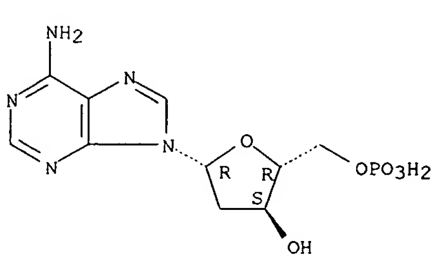
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



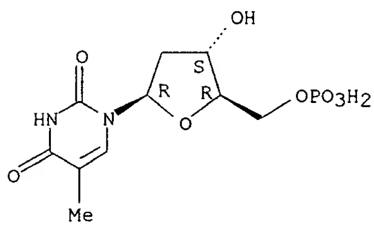
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.

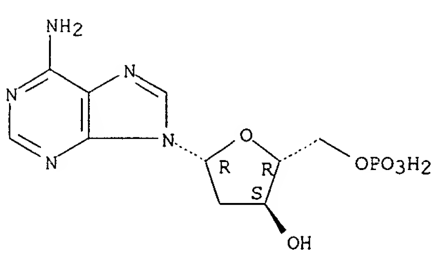


IT **25191-20-2**, Poly(dA)
RL: BIOL (Biological study)
(quinolone antibacterials binding to, **DNA** gyrase inhibition mechanism in relation to)
RN 25191-20-2 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



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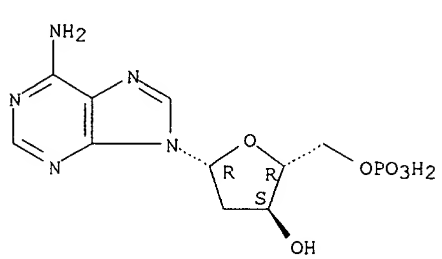
L30 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:593915 HCAPLUS
DN 107:193915
TI Efficiency of the **complex** formation between nucleotides and human DNA polymerase .alpha.. Enzyme modification by chemically reactive nucleotide analogs
AU Nevinskii, G. A.; Doronin, S. V.; Podust, V. N.; Lavrik, O. I.
CS Inst. Bioorg. Chem., Novosibirsk, USSR
SO Mol. Biol. (Moscow) (1987), 21(4), 1070-9
CODEN: MOBIBO; ISSN: 0026-8984
DT Journal
LA Russian
AB The modification of the human placenta DNA polymerase .alpha. by **imidazolides** (Im) of deoxynucleoside monophosphates (dNMPs) was investigated. The modification occurs only in the simultaneous presence of template and primer. This process, however, doesn't depend on the complementary interaction of the nucleotide base with the template. The dissocn. const. (Kd) values of the **complexes** between the different nucleotides and DNA polymerase .alpha. were estd. The affinity of Im-dTMP was detd. from the dependence of the apparent rate const. of enzyme inactivation on the reagent concn. The Kd values for dNMP, dNDP, and dNTP (where N is any nucleoside) were estd. by using the protective effect of these nucleotides against enzyme modification by Im-dTMP. The comparison of the interaction efficiency between the polymerase and dNMP, dNDP, or dNTP (complementary or noncomplementary to the template) indicate that the nucleotide discrimination occurs on the dNTP level, i.e. dNMP and dNDP don't interact with complementarily with the template in the enzyme **complex**. The addnl. contacts between the enzyme and the nucleotide terminal phosphate are presumed to form only for the complementary dNTP. A hypothetical model of the template-complementary dNTP binding to the polymerases is advanced. The role of the hydrophobic interaction of the nucleotides with the enzyme as well as the possible influence of the nucleotide .gamma.-phosphate group on the template-dNTP complement formation is discussed. The Watson-Crick bond formation between the nucleotide and the template is followed by an addnl. conformational rearrangement of the nucleotide triphosphate chain, which in turn leads to the formation of addnl. contacts between the enzyme and the nucleotide .gamma.-phosphate.
IT **25191-20-2**, Poly(dA)
RL: BIOL (Biological study)
(**DNA** polymerase .alpha. of human **complex** formation with deoxynucleotides in presence of, efficiency of)
RN 25191-20-2 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



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L30  ANSWER 9 OF 15  HCAPLUS  COPYRIGHT 2000 ACS
AN   1986:47676  HCAPLUS
DN   104:47676
TI   E. coli DNA polymerase I:  primer-template-dependent enzyme inactivation
     by imidazolides of deoxynucleoside 5'-triphosphates
AU   Nevinskii, G. A.; Doronin, S. V.; Lavrik, O. I.
CS   Inst. Bioorg. Chem., Novosibirsk, USSR
SO   Biopolim. Kletka (1985), 1(5), 247-53
     CODEN: BIKLEK
DT   Journal
LA   Russian
AB   The interaction of Escherichia coli DNA polymerase I with
     imidazolides of dATP, dCTP, dGTP, and dTTP was investigated in the
     presence and the absence of different primer-template complexes.
     The enzyme can be inactivated by the imidazolides only in the
     presence of a primer and a template which is complementary to the
     deoxyribonucleoside triphosphate analog.  Apparently, the orientation of
     the analog's polyphosphate chain changes due to analog-template
     complex formation.
IT   25191-20-2
     RL: BIOL (Biological study)
        (DNA polymerase I inactivation by deoxynucleoside
        triphosphate imidazolides in presence of, primer-template
        dependence of inactivation in relation to)
RN   25191-20-2  HCAPLUS
CN   5'-Adenylic acid, 2'-deoxy-, homopolymer (9CI)  (CA INDEX NAME)

     CM   1

     CRN  653-63-4
     CMF  C10 H14 N5 O6 P

Absolute stereochemistry.  Rotation (+).
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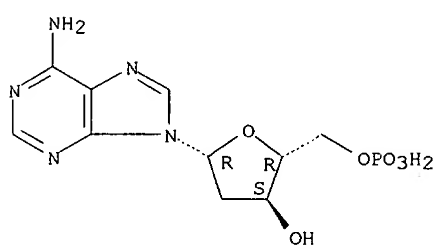


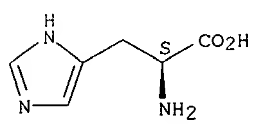
=> d bib abs hitstr l30 10

L30 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:30291 HCAPLUS
DN 96:30291
TI Study of poly-L-**histidine** **complexes** with DNA by hyperchromic spectra
AU Raim, T.; Raukas, E.
CS Inst. Exp. Biol., Harku, USSR
SO Mol. Biol. (Moscow) (1981), 15(6), 1342-9
CODEN: MOBIBO; ISSN: 0026-8984
DT Journal
LA Russian
AB **Complexes** of DNA with poly(L-**histidine**) in acidic media were investigated by hyperchromic spectroscopy. Based on least squares methods, the hyperchromic spectra were resolved into components corresponding to the melting of AT and GC base pairs and protonation of cytosine. The protonation of cytosine was proportional to the fraction of melted GC base pairs and was not influenced by the presence of poly(L-**histidine**). Selectivity of poly(L-**histidine**) towards the base pairs was very weak or absent.
IT **26062-48-6D, DNA complexes 26854-81-9D**
, DNA complexes
RL: PRP (Properties)
(structure of)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

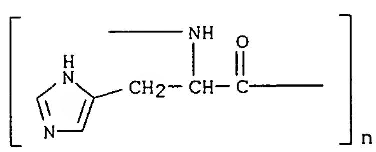
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



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L30 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1981:493250 HCAPLUS
DN 95:93250
TI Mechanism of recognition of AT pairs in DNA by "Hoechst 33258" dye
AU Mikhailov, M. V.; Zasedatelev, A. S; Krylov, A. S.; Gurskii, G. V.
CS Inst. Mol. Biol., Moscow, USSR
SO Mol. Biol. (Moscow) (1981), 15(3), 690-705
CODEN: MOBIBO; ISSN: 0026-8984
DT Journal
LA Russian
AB A mol. model of the **complex** between the AT-specific dye Hoechst 33258 and DNA was proposed based on the exptl. data. According to the model, the dye is localized tightly in a DNA slot engaging 4 base pairs. The **benzimidazole** skeleton of the bound dye forms a helix, isogeometric with the B form of DNA. The AT-specific binding of the dye with DNA is due to H bonding between the dye and the AT pairs. The donors for H bonding are the NH groups of **benzimidazole** and 1 CH3NH+-group of the N-methylpiperazine portion of the dye and the acceptors-atoms of O-2 of thymine and(or) N-3 of adenine. The energy of interaction between the dye and DNA is markedly reduced when the binding portion contains GC pairs. In this case, the amino group in the 2nd position of guanine sterically prevents H-bond formation with N-3 and also inhibits (partially or totally) formation of a H bond with O-2 of cytosine.
IT **24939-09-1**
RL: ANST (Analytical study)
(adenine-thymine base pairs detection in **DNA** by Hoechst 33258 in relation to)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

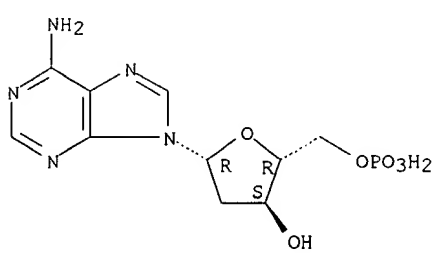
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



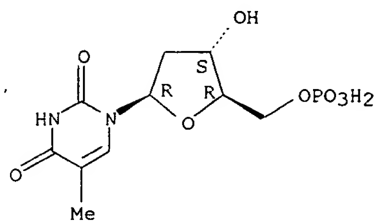
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

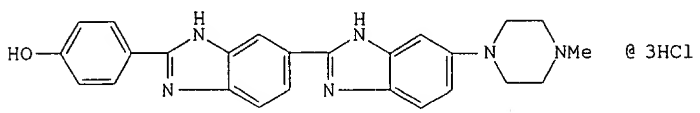
CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.



=> d bib abs hitstr l30 12

L30 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1981:98170 HCAPLUS
DN 94:98170
TI Mechanism of the "recognition" of AT pairs in DNA by molecules of Hoechst 33258 dye
AU Zasedatelev, A. S.; Mikhailov, M. V.; Krylov, A. S.; Gurskii, G. V.
CS Inst. Mol. Biol., Moscow, USSR
SO Dokl. Akad. Nauk SSSR (1980), 255(3), 756-60 [Biochem.]
CODEN: DANKAS; ISSN: 0002-3264
DT Journal
LA Russian
GI



I

AB CD and optical d. data on the binding of Hoechst dye 33258 (I) to DNA and polydeoxyribonucleotides indicate that the dye lies in the narrow groove of DNA and occupies 4 base pairs; the dye **benzimidazole** forms a spiral isogeometric with the B form of DNA. Adenine-thymine specific binding is ensured by H bonding between these base pairs and the dye mol. The dye **benzimidazole** NH groups and a CH3N+H group of the N-methylpiperazine residue serve as H donors and the O2 of thymine and N3 of adenine as H acceptors. This model is supported by (1) dye binding of poly(dI-dC).cntdot.poly(dI-dC) and poly(dA-dT).cntdot.poly(dA-dT) which have the same functional groups only in the narrow groove; (2) lack of binding with guanine-cytosine polymers; (3) dye binding with phage T6 DNA which has an inaccessible wide groove due to the presence of glucose or diglucose residues; (4) lack of dye binding to DNA satd. with the narrow-groove binding antibiotic distamycin A; (5) lack of binding with double-stranded RNA or A form DNA; (6) no increase in viscosity as would be expected with intercalating compds.; and (7) resistance of the DNA-dye **complexs** to LiCl and dissocn. of the **complex** in 4.5M guanidine, an H bond breaking agent.
IT **24939-09-1**
RL: BIOL (Biological study)
(Hoechst dye 33258 binding of, **DNA** binding model in relation to)
RN 24939-09-1 HCAPLUS
CN 5'-Adenylic acid, 2'-deoxy-, homopolymer, complex with 5'-thymidylic acid homopolymer (1:1) (9CI) (CA INDEX NAME)

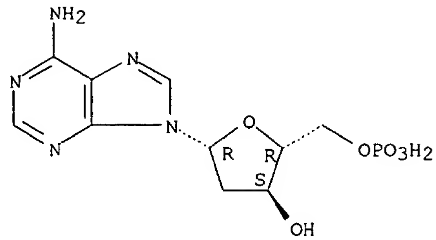
CM 1

CRN 25191-20-2
CMF (C10 H14 N5 O6 P)x
CCI PMS

CM 2

CRN 653-63-4
CMF C10 H14 N5 O6 P

Absolute stereochemistry. Rotation (+).



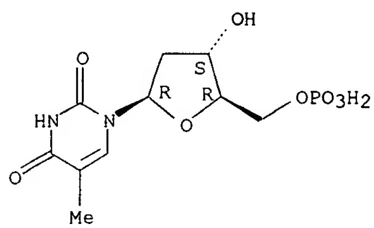
CM 3

CRN 25086-81-1
CMF (C10 H15 N2 O8 P)x
CCI PMS

CM 4

CRN 365-07-1
CMF C10 H15 N2 O8 P
CDES 5:B-D-ERYTHRO

Absolute stereochemistry.



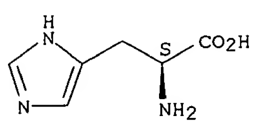
=> d bib abs hitstr l30 13

L30 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:606048 HCAPLUS
DN 91:206048
TI DNA aggregation by poly-L-**histidine**
AU Brini, M'hamed
CS Ec. Norm. Super., Le Bardo, Tunisia
SO Ec. Fr.-Maghrebine Printemps Biol. Mol., [C. R.], 1st (1978), 133-6.
Editor(s): Ben-Hamida, Fakher. Publisher: Fakher Ben-Hamida, c/o Inst.
Rech. Biol. Mol. CNRS, Paris, Fr.
CODEN: 41SYAJ
DT Conference
LA French
AB The secondary structure of the condensed B form of DNA in 2M NaCl was altered by assocn. with poly-L-**histidine** (I), as shown by changes in the UV absorption and CD spectra of the mols. The intensity of the CD bands of the DNA-polypeptide **complex** was much greater than that of DNA alone. An intense neg. band at 270 nm suggested a structure for the DNA like that (the .PSI. state) adopted in polyethylene glycol-salt solns., and electron microscopy showed .PSI.-like toroidal structures in the DNA-I prepns. However, the DNA-I **complexes** differed from .PSI.-form DNA by having a pos. CD band reminiscent of the 275-nm band of the DNA-histone F2b **complex**.
IT **26062-48-6D, DNA complexes 26854-81-9D**
, DNA complexes
RL: PRP (Properties)
(properties of)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

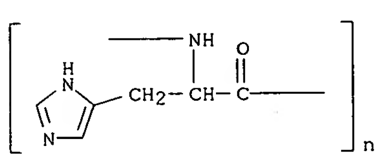
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI)
(CA INDEX NAME)



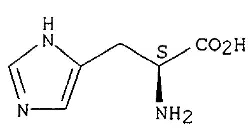
=> d bib abs hitstr l30 14

L30 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:46550 HCAPLUS
DN 88:46550
TI Thermal denaturation of DNA **complexes** with poly-L-**histidine** and poly-L-lysine depending on pH
AU Kooli, K.; Raim, T.; Raukas, E.
CS Inst. Exp. Biol., Harku, USSR
SO Stud. Biophys. (1978), 67, 77-8
CODEN: STBIBN
DT Journal
LA English
AB The interaction of poly-L-lysine (I) with DNA was studied as a function of the ionization of NH2 groups and the conformation of I in the pH range 8-10. The conformation of I in the **complex** with DNA was apparently entirely detd. by interaction between NH2 and phosphate groups, irresp. of the I original conformation and the degree of ionization (at pH .ltoreq.10), and the stoichiometry of the **complex** did not depend on the conformation of I. In poly-L-**histidine** (II) **complexes** with DNA in NaCl solns. at pH 5, melting profiles showed that the protonation of cytosine increased proportionally to the fraction of disrupted G-C base pairs. The interaction of II and DNA under these conditions was nonspecific.
IT **26062-48-6D, DNA complexes 26854-81-9D, DNA complexes**
RL: BIOL (Biological study)
(thermal denaturation of, pH effect on)
RN 26062-48-6 HCAPLUS
CN L-Histidine, homopolymer (9CI) (CA INDEX NAME)

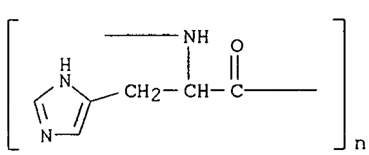
CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

Absolute stereochemistry. Rotation (-).



RN 26854-81-9 HCAPLUS
CN Poly[imino[(1S)-1-(1H-imidazol-4-ylmethyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



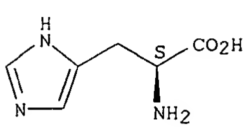
=> d bib abs hitstr 130 15

L30 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1977:563024 HCAPLUS
DN 87:163024
TI Interaction between poly(L-lysine48, L-**histidine52**) and DNA
AU Santella, Regina M.; Li, Hsueh Jei
CS Dep. Chem., City Univ. New York, Brooklyn, N. Y., USA
SO Biopolymers (1977), 16(9), 1879-94
CODEN: BIPMAA
DT Journal
LA English
AB The title copolymer (I), a random copolypeptide of L-lysine and L-**histidine,** was used a model protein for investigating the effects of protonation on the **imidazole** group of **histidines** on protein binding to DNA. The **complexes** formed between I and DNA were examd. using absorbance, CD, and thermal denaturation. Although increasing pH reduces the charges on **histidine** side chains in the model protein, I still binds the DNA with .apprx.1 pos. charge/neg. charge in protein-bound regions. Nevertheless, CD and melting properties of I-DNA **complexes** still depend upon the soln. pH which dets. the protonation state of the **imidazole** group of **histidine** side chains. Presumably, the presence of deprotonated **histidine** residues destabilizes the native structure of protein-bound DNA. The binding of I to DNA causes a red shift of the crossover point and both a red shift and a redn. of the pos. CD band of DNA near 275 nm. These effects, however, are greatly diminished when **histidine** side chains in the model protein are deprotonated. The structure of already formed I-DNA **complexes** can be perturbed by changing the soln. pH. However, the results suggest a readjustment of the **complex** to accommodate charge interactions rather than a full dissocn. of the **complex** followed by reassocn. between the model protein and DNA.
IT **31014-77-4**
RL: BIOL (Biological study)
(**DNA** binding by, **histidine** protonation effect on)
RN 31014-77-4 HCAPLUS
CN L-Histidine, polymer with L-lysine (9CI) (CA INDEX NAME)

CM 1

CRN 71-00-1
CMF C6 H9 N3 O2

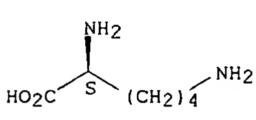
Absolute stereochemistry. Rotation (-).



CM 2

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



#1 TEXT & INVENTOR SEARCH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=> d his

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     FILE 'HCAPLUS' ENTERED AT 13:44:32 ON 28 OCT 2000
L1          66 S MIDOUX P?/AU
L2         279 S MONSIGNY M?/AU
L3          66 S L1 AND L2
L4          22 S L3 AND COMPLEX?
L5           6 S L4 AND ?POLYMER?
L6          16 S L4 NOT L5
L7          11 S L4 AND (HISTIDIN? OR ?AMINE OR IMIDAZOL?)
L8          20 S L6 OR L7
               SELECT RN L8 1-20

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     FILE 'HCAPLUS' ENTERED AT 13:52:47 ON 28 OCT 2000
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L13    1219338 S CONJUGAT? OR COMPLEX?
L14    1281714 S POLYMER? OR POLYLYS? OR POLYAMIN? OR AMINE(5A)POLYMER?
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L17      25558 S FREE(5A)(AMINO OR AMMON? OR "NH3+")
L18         17 S L16(L)L17
L19     427655 S ?HISTIDIN? OR ?IMIDAZOL? OR ?QUINOLIN? OR ?PTERIN? OR ?PYRIDI
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L21          1 S L20 AND L18
L22          0 S L21 NOT L8
L23       3141 S FREE(5A)AMINE?
L24          6 S L23 AND L16
L25          6 S L24 NOT L8
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L29         19 S L28 NOT L8
L30          6 S L29 AND PY>1997
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L32       1662 S L14 AND (L23 OR L17)
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L36          6 S L33 AND L35
L37        586 S L15 AND ?TRANSFECT?
L38          6 S L32 AND L37
L39          6 S L37 AND  (L23 OR L17)
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L41      27856 S L34(L)L14
L42       1280 S L40 AND L41
L43       1169 S L40(L)L41
L44          1 S L42 AND (L17 OR L23)
L45          1 S L44 NOT L8   1 cite
L46      29254 S ?TRANSFECT? AND L12
L47       3569 S ?TRANSFECT? AND L14
L48       2527 S L46 AND L47
L49          7 S L48 AND (L17 OR L23)
L50         51 S L48 AND L19
L51         42 S (L50 OR L35) AND (L13 OR ASSOCIAT?)
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L56         11 S L55 NOT ASSOCIAT?/TI   11 cites

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INVENTOR SEARCH

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L58      614290 S POLYMER? OR POLYLYS? OR POLYAMIN? OR AMINE(5A)POLYMER?
L59      929929 S CONJUGAT? OR COMPLEX?
L60       10355 S L57(P)L58(P)L59
L61       32104 S FREE(5A)(AMINO OR AMMON? OR "NH3+" OR AMINE)
L62         430 S L60 AND L61
L63         362 S L62 AND (?MEMBRAN? OR TRANSFECT?)
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L65         304 S L63 AND L64
L66         304 DUP REM L65 (0 DUPLICATES REMOVED)
L67          26 S L60(P)L61
L68          16 S L64 AND L67
L69          16 DUP REM L68 (0 DUPLICATES REMOVED)
L70          17 S L63 AND L67
L71       21456 S ?MEMBRAN?(5A)(?STABIL? OR ?STABL? OR DISRUPT? OR  PENETRAT?)
L72          34 S L71 AND L65
L73          57 S L72 OR L70 OR L67
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57 cites – selected cites displayed; continuations & divisionals not displayed

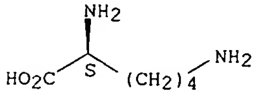
=> d bib abs hitstr l10 1

L10 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:138249 HCAPLUS
DN 132:269966
TI Efficient gene transfer into human normal and cystic fibrosis tracheal gland serous cells with synthetic vectors
AU Allo, Jean-Christophe; **Midoux, Patrick**; Merten, Marc; Souil, Evelyne; Lipecka, Joanna; Figarella, Catherine; **Monsigny, Michel** ; Briand, Pascale; Fajac, Isabelle
CS INSERM U380, ICGM, INSERM U380, ICGM, Universite Rene Descartes (Paris V), Paris, 75014, Fr.
SO Am. J. Respir. Cell Mol. Biol. (2000), 22(2), 166-175
CODEN: AJRBEL; ISSN: 1044-1549
PB American Thoracic Society
DT Journal
LA English
AB Submucosal gland serous cells are believed to play a major role in the physiopathol. of cystic fibrosis (CF) and may represent an important target for CF gene therapy. We have studied the efficiency of reporter gene transfer into immortalized normal (MM-39) and CF (CF-KM4) human airway epithelial gland serous cells using various synthetic vectors: glycosylated polylysines (glycofectins), polyethylenimine (PEI) (25 and 800 kD), lipofectin, and **lipofectAMINE**. In both cell lines, a high luciferase activity was achieved with various glycofectins, with PEI 25 kD, and with **lipofectAMINE**. After three transfections applied daily using .alpha.-glycosylated polylysine, 20% of the cells were transfected. At 24 h after CF transmembrane conductance regulator (CFTR) gene transfer into CF-KM4 cells using .alpha.-glycosylated polylysine, the immunolocalization of CFTR was analyzed by laser scanning confocal microscopy and the transgenic CFTR was detected by an intense labeling of the plasma membrane. The presence of membrane lectins, i.e., cell surface receptors binding oligosaccharides, was also examd. on MM-39 and CF-KM4 cells by assessing the binding and uptake of fluorescein-labeled neoglycoproteins and fluorescein-labeled glycoplexes (glycofectins **complexed** to plasmid DNA). Among all the neoglycoproteins and glycoplexes tested, those bearing .alpha.-mannosylated derivs. were most efficiently taken up by both normal and CF gland serous cells. However, .alpha.-mannosylated polylysine was quite inefficient for gene transfer, indicating that the efficiency of gene transfer is detd. both by the uptake of the **complexes** and also by their intracellular trafficking. Moreover, our results show that an efficient in vitro gene transfer was achieved in human airway gland serous cells with the same synthetic vectors described to efficiently transfect human airway surface epithelial cells.
IT **25104-18-1D**, Polylysine, glycosylated
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
((glycofectins); efficient gene transfer into human normal and cystic fibrosis tracheal gland serous cells with synthetic vectors)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



IT **9002-98-6**, Polyethylenimine **128835-92-7**, Lipofectin **158571-62-1**, **LipofectAMINE**

RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(efficient gene transfer into human normal and cystic fibrosis tracheal gland serous cells with synthetic vectors)

RN 9002-98-6 HCAPLUS
CN Aziridine, homopolymer (9CI) (CA INDEX NAME)

CM 1

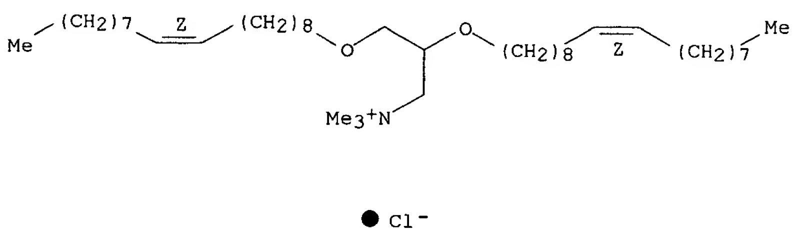
CRN 151-56-4
CMF C2 H5 N

RN 128835-92-7 HCAPLUS
CN 1-Propanaminium, N,N,N-trimethyl-2,3-bis[(9Z)-9-octadecenyloxy]-, chloride, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 104162-48-3
CMF C42 H84 N O2 . Cl
CDES 2:Z,Z

Double bond geometry as shown.

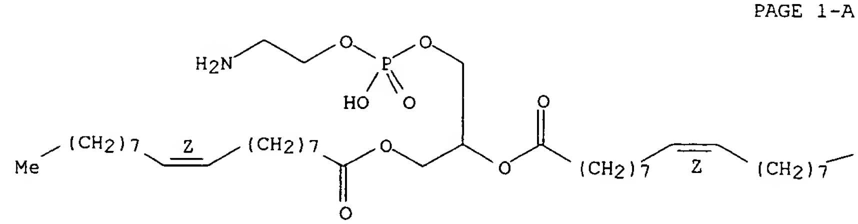


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

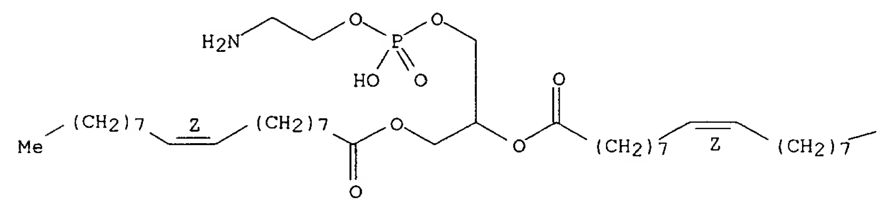
RN 158571-62-1 HCAPLUS
CN 1-Propanaminium, N-[3-[[3-[[4-[(3-aminopropyl)amino]butyl]amino]propyl]amino]-3-oxopropyl]-N,N-dimethyl-2,3-bis[[(9Z)-1-oxo-9-octadecenyl]oxy]-, salt with trifluoroacetic acid (1:1), mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

CM 2

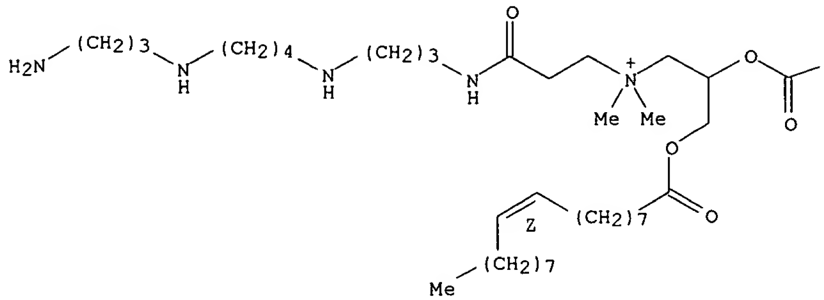
CRN 185097-43-2
CMF C54 H106 N5 O5 . C2 F3 O2

CM 3

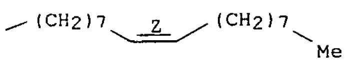
CRN 181508-68-9
CMF C54 H106 N5 O5
CDES 2:Z,Z

Double bond geometry as shown.

PAGE 1-A

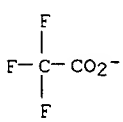


PAGE 1-B



CM 4

CRN 14477-72-6
CMF C2 F3 O2

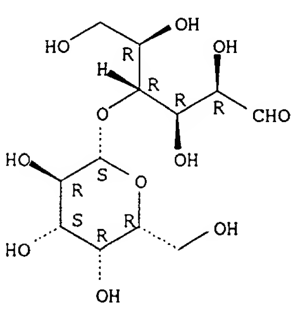


RE.CNT 34
RE
(1) Barasch, J; Nature 1991, V352, P70 HCAPLUS
(2) Biwersi, J; Proc Natl Acad Sci USA 1996, V93, P12484 HCAPLUS
(3) Boussif, O; Proc Natl Acad Sci USA 1995, V92, P7297 HCAPLUS
(4) Bradbury, N; Science 1992, V256, P530 HCAPLUS
(5) Curiel, D; Am J Respir Cell Mol Biol 1996, V14, P1 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l10 2

L10 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:384569 HCAPLUS
DN 131:219069
TI Glycofection in the presence of anionic fusogenic peptides: A study of the parameters affecting the peptide-mediated enhancement of the transfection efficiency
AU Kichler, Antoine; Freulon, Isabelle; Boutin, Valerie; Mayer, Roger; **Monsigny, Michel; Midoux, Patrick**
CS Glycobiologie, Centre de Biophysique Moleculaire, Orleans, F-45071, Fr.
SO J. Gene Med. (1999), 1(2), 134-143
CODEN: JGMEFG; ISSN: 1099-498X
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Gene delivery mediated by polyplexes such as DNA **complexed** with polylysine conjugates is limited by the low efficiency of escape of DNA from the endosomes. One of the strategies which favors the transmembrane passage of polyplexes consists of adding anionic amphipathic peptides capable of destabilizing membranes in an acidic medium. Although less efficient than replication-defective adenoviruses, fusogenic peptides increase the expression of the reporter gene by a factor between 100 and 1000 depending on the cell line. However, the activity of a given peptide depends on the compn. of the lipid bilayer. We were interested in developing a polyplex (glycoplex) formulation comprising a glycosylated polylysine, a fusogenic peptide and a plasmid which would be useful for efficient transfection (glycofection) of a large panel of cells, even in the presence of serum. We synthesized several peptides and tested their efficiency in combination with different glycoplex formulations. We found that glycofection with a quaternary **complex** (called one pot formulation) made of lactosylated-polylysine, polylysine, DNA, and the dimeric peptide (E5-WYGG)2-KA was less cell-type dependent than other peptide-based formulations. In addn., its efficiency was not affected by the presence of serum (up to 20%).
IT **63-42-3D**, Lactose, reaction products with poly-L-lysine, DNA conjugates **25104-18-1D**, Poly-L-lysine, lactosylation products, DNA **complexes** **38000-06-5D**, Poly-L-lysine, lactosylation products, DNA **complexes**
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(glycofection in the presence of anionic fusogenic peptides)
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

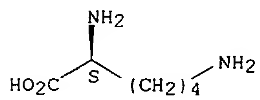


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

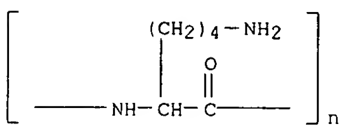
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



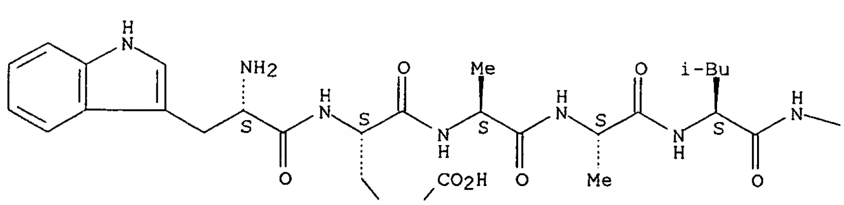
RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



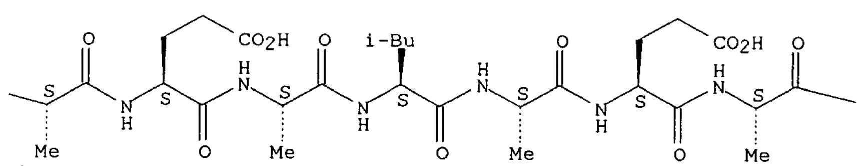
IT **107658-43-5D,** conjugates **171117-66-1D,** conjugates **243133-42-8D,** conjugates **243448-64-8D,** conjugates
RL: PRP (Properties)
(glycofection in the presence of anionic fusogenic peptides)
RN 107658-43-5 HCAPLUS
CN L-Alanine, L-tryptophyl-L-.alpha.-glutamyl-L-alanyl-L-alanyl-L-leucyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-leucyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-leucyl-L-alanyl-L-.alpha.-glutamyl-L-histidyl-L-leucyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-leucyl-L-alanyl-L-.alpha.-glutamyl-L-alanyl-L-leucyl-L-.alpha.-glutamyl-L-alanyl-L-leucyl-L-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

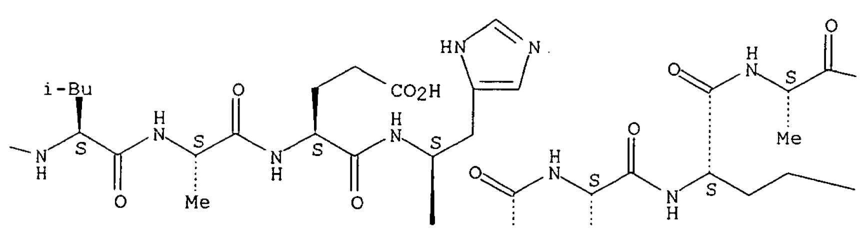
PAGE 1-A



PAGE 1-B



PAGE 1-C



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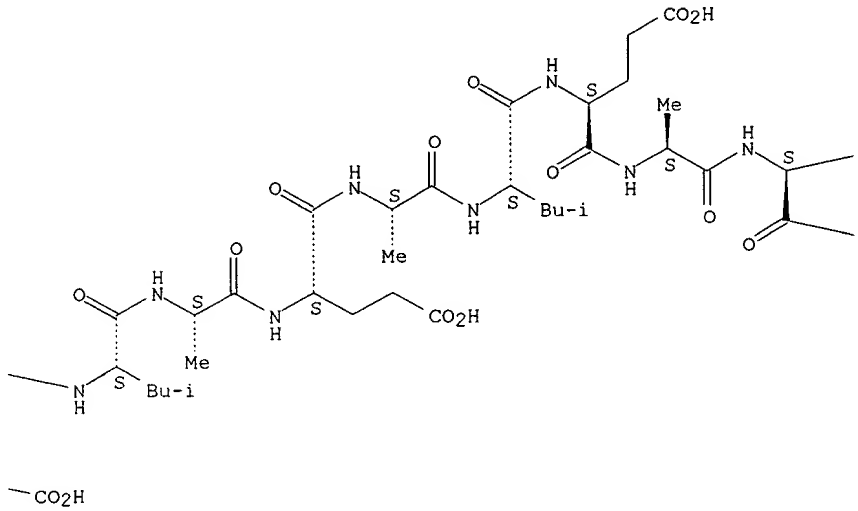
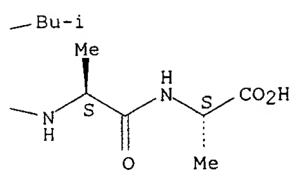
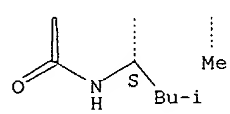


PAGE 1-E



PAGE 2-A

PAGE 2-C

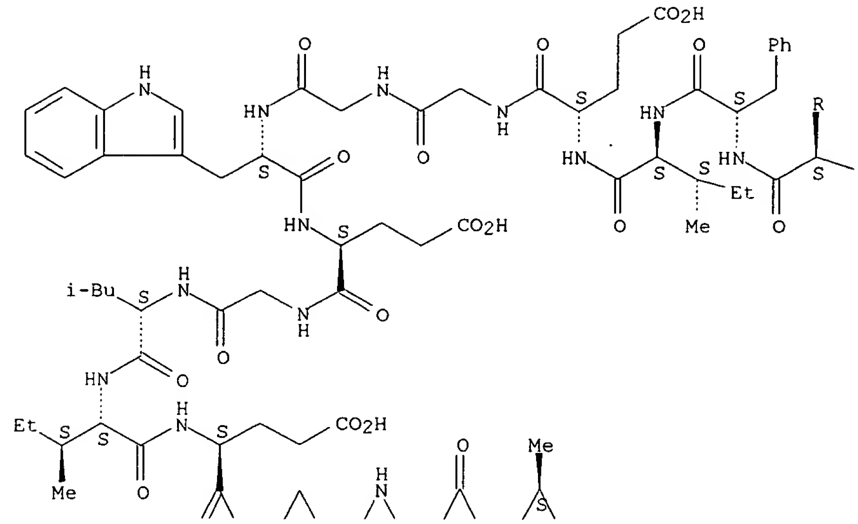


RN 171117-66-1 HCAPLUS

CN L-Alanine, glycyl-L-leucyl-L-phenylalanyl-L-.alpha.-glutamyl-L-alanyl-L-isoleucyl-L-alanyl-L-.alpha.-glutamyl-L-phenylalanyl-L-isoleucyl-L-.alpha.-glutamylglycylglycyl-L-tryptophyl-L-.alpha.-glutamylglycyl-L-leucyl-L-isoleucyl-L-.alpha.-glutamylglycyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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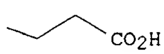
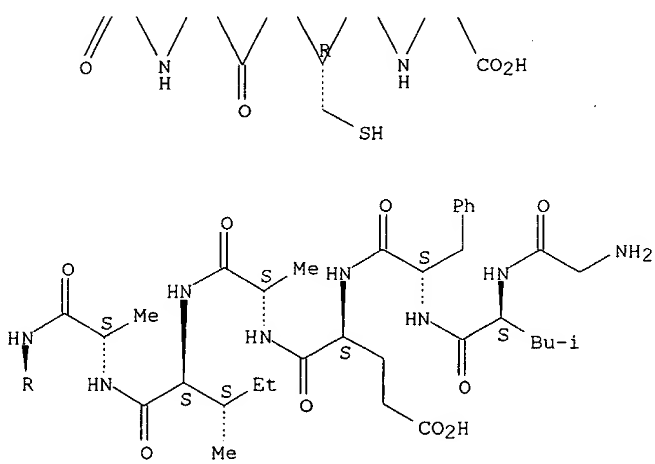


PAGE 2-A

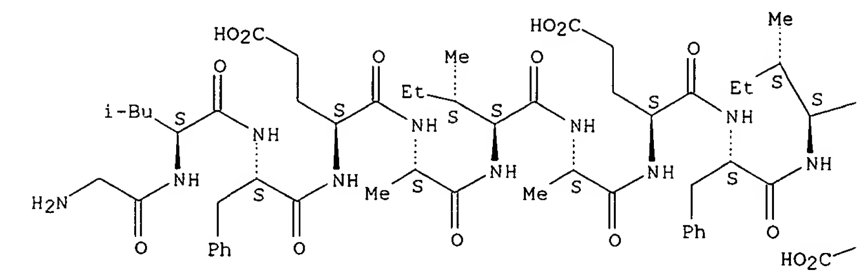


RN 243133-42-8 HCAPLUS
CN Glycine, glycyl-L-leucyl-L-phenylalanyl-L-.alpha.-glutamyl-L-alanyl-L-isoleucyl-L-alanyl-L-.alpha.-glutamyl-L-phenylalanyl-L-isoleucyl-L-.alpha.-glutamylglycylglycyl-L-tryptophyl-L-.alpha.-glutamylglycyl-L-leucyl-L-

isoleucyl-L-.alpha.-glutamylglycyl-L-tryptophyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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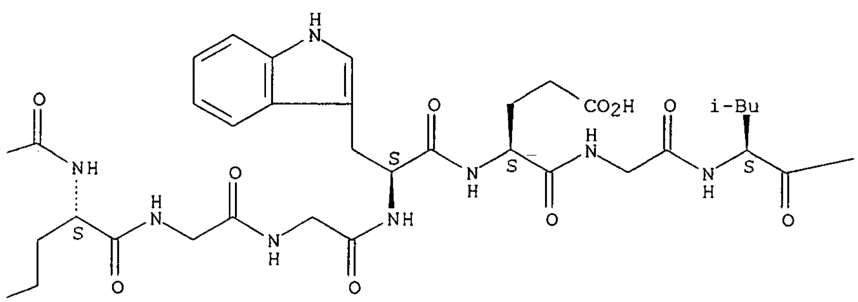
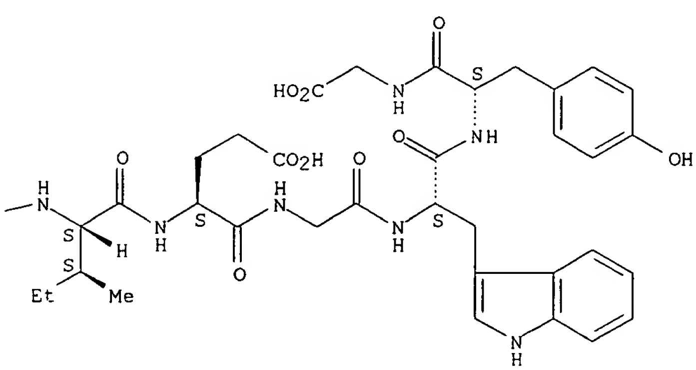


PAGE 1-C



RN 243448-64-8 HCAPLUS

CN L-Alanine, N2,N6-bis(glycyl-L-leucyl-L-phenylalanyl-L-.alpha.-glutamyl-L-alanyl-L-isoleucyl-L-alanyl-L-.alpha.-glutamyl-L-phenylalanyl-L-isoleucyl-

L-.alpha.-glutamylglycylglycyl-L-tryptophyl-L-.alpha.-glutamylglycyl-L-leucyl-L-isoleucyl-L-.alpha.-glutamylglycyl-L-tryptophyl-L-tyrosylglycylglycyl)-L-lysyl- (9CI) (CA INDEX NAME)

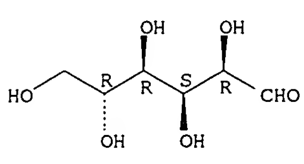
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 34
RE

(1) Boussif, O; Proc Natl Acad Sci U S A 1995, V92, P7297 HCAPLUS
(2) Bowman, E; Proc Natl Acad Sci U S A 1988, V85, P7972 HCAPLUS
(3) Curiel, D; Proc Natl Acad Sci U S A 1991, V88, P8850 HCAPLUS
(4) De Wet, J; Mol Cell Biol 1987, V7, P725 HCAPLUS
(5) Derrien, D; Glycoconjugate J 1989, V6, P241 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l10 3

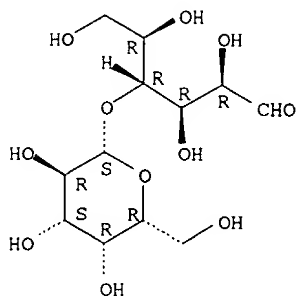
L10 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:168321 HCAPLUS
DN 130:357040
TI Glycofection: the ubiquitous roles of sugar bound on glycoplexes
AU Boutin, Valerie; Legrand, Alain; Mayer, Roger; Nachtigal, Maurice; **Monsigny, Michel; Midoux, Patrick**
CS Glycobiology Centre de Biophysique Moleculaire, CNRS UPR4301, University of Orleans, Orleans, F-45071, Fr.
SO Drug Delivery (1999), 6(1), 45-50
CODEN: DDELEB; ISSN: 1071-7544
PB Taylor & Francis
DT Journal
LA English
AB Glycofection (transfection by using sugar-substituted polylysine) was assessed in order to provide an alternative to viral vectors for the transfer of genes into vascular smooth muscle cells. A rabbit vascular smooth muscle cell line (Rb-1 cells) was selectively transfected by using glycoplexes (glycosylated polylysine/pSV2LUC **complexes**) in the presence of 10 .mu.M of the fusogenic peptide GALA. A sugar-specific transfection was obtained when the glycofection was conducted for 1 h with glycoplexes contg. either .alpha.-Gal, .alpha.-Glc, .alpha.-GalNAc, .beta.-GlcNAc, or .beta.-GalNAc residues. The gene expression was high after transfection, with glycoplexes bearing .alpha.-Gal, .alpha.-GalNAc, or .beta.-GalNAc residues that were weakly internalized, and low with glycoplexes carrying Lact or Rha residues that were well taken up by cells. These results suggest that 1) glycofection can be a good approach for a selective transfer of genes into vascular smooth muscle cells, 2) an efficient uptake of the glycoplexes is not the unique limiting step for an efficient transfection, and 3) the sugar-dependent trafficking of the glycoplexes inside the cells may account for the transfection efficiency.
IT **50-99-7DP**, D-Glucose, polylysine conjugates **63-42-3DP**, polylysine conjugates **2438-80-4DP**, L-Fucose, polylysine conjugates **3458-28-4DP**, D-Mannose, polylysine conjugates **3615-41-6DP**, L-Rhamnose, polylysine conjugates **10257-28-0DP**, D-Galactopyranose, polylysine conjugates **14131-60-3DP**, .beta.-D-Galactopyranose, 2-(acetylamino)-2-deoxy-, polylysine conjugates **14131-68-1DP**, polylysine conjugates **14215-68-0DP**, 2-Acetamido-2-deoxy-.alpha.-D-galactopyranose, polylysine conjugates **25104-18-1DP**, Poly-L-lysine, sugar conjugates **38000-06-5DP**, Poly-L-lysine, sugar conjugates
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(glycofection for transfection of vascular smooth muscle)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



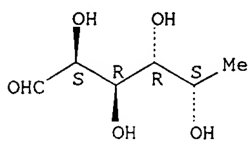
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



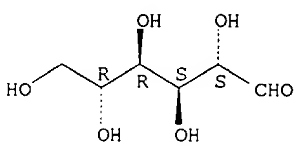
RN 2438-80-4 HCAPLUS
CN L-Galactose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



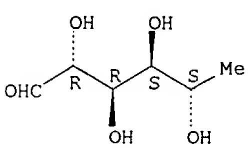
RN 3458-28-4 HCAPLUS
CN D-Mannose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



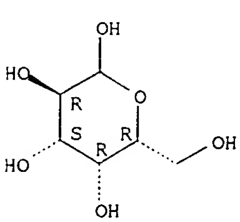
RN 3615-41-6 HCAPLUS
CN L-Mannose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



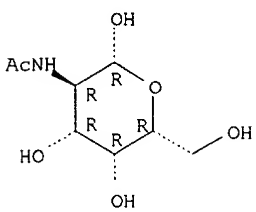
RN 10257-28-0 HCAPLUS
CN D-Galactopyranose (9CI) (CA INDEX NAME)

Absolute stereochemistry.



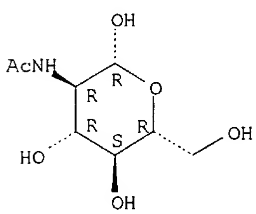
RN 14131-60-3 HCAPLUS
CN .beta.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



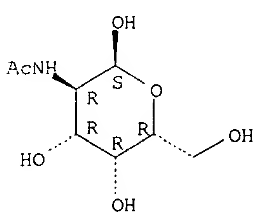
RN 14131-68-1 HCAPLUS
CN .beta.-D-Glucopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 14215-68-0 HCAPLUS
CN .alpha.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

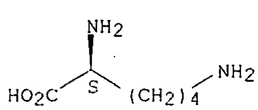


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

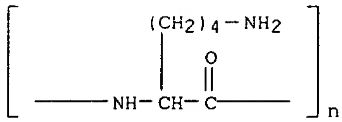
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RE.CNT 41
RE
(1) Brasier, A; BioTechniques 1989, V7, P1116 HCAPLUS
(2) Chang, M; J Clin Invest 1995, V96, P2260 HCAPLUS
(3) Chang, M; Mol Med 1995, V1, P172 HCAPLUS
(4) Channon, K; Cardiovasc Res 1996, V32, P962 HCAPLUS
(7) de Wet, J; Mol Cell Biol 1987, V7, P725 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

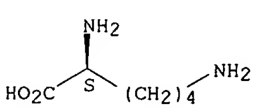
=> d bib abs hitstr l10 4

L10 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:161559 HCAPLUS
DN 131:28442
TI Efficient Gene Transfer by Histidylated Polylysine/pDNA **Complexes**
AU **Midoux, Patrick; Monsigny, Michel**
CS Centre de Biophysique Moleculaire Glycobiologie CNRS UPR4301, University of Orleans, Orleans, F-45071, Fr.
SO Bioconjugate Chem. (1999), 10(3), 406-411
CODEN: BCCHES; ISSN: 1043-1802
PB American Chemical Society
DT Journal
LA English
AB Plasmid/polylysine **complexes,** which are used to transfect mammalian cells, increase the uptake of DNA, but plasmid mols. are sequestered into vesicles where they cannot escape to reach the nuclear machinery. However, the transfection efficiency increases when membrane-disrupting reagents such as chloroquine or fusogenic peptides, are used to disrupt endosomal membranes and to favor the delivery of plasmid into the cytosol. We designed a cationic polymer that forms **complexes** with a plasmid DNA (pDNA) and mediates the transfection of various cell lines in the absence of chloroquine or fusogenic peptides. This polymer is a polylysine (av. d.p. of 190) partially substituted with histidyl residues which become cationic upon protonation of the **imidazole** groups at pH below 6.0. The transfection efficiency was optimal with a polylysine having 38.+-.5% of the .epsilon.-amino groups substituted with histidyl residues; it was not significantly impaired in the presence of serum in the culture medium. The transfection was drastically inhibited in the presence of bafilomycin A1, indicating that the protonation of the **imidazole** groups in the endosome lumen might favor the delivery of pDNA into the cytosol.
IT **25104-18-1**, Polylysine
RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(histidylated, **complex** with plasmid DNA; efficient gene transfer by histidylated polylysine/pDNA **complexes**)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.

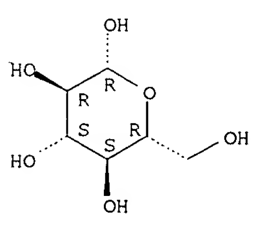


RE.CNT 29
RE
(1) Boussif, O; Proc Natl Acad Sci U S A 1995, V92, P7297 HCAPLUS
(2) Bowman, E; Proc Natl Acad Sci U S A 1988, V85, P7972 HCAPLUS
(6) de Wet, J; Mol Cell Biol 1987, V7, P725 HCAPLUS
(7) Derrien, D; Glycoconjugate J 1989, V6, P241 HCAPLUS
(8) Erbacher, P; Exp Cell Res 1996, V225, P186 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l10 5

L10 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:123664 HCAPLUS
DN 130:307274
TI Sugar-mediated uptake of glycosylated polylysines and gene transfer into normal and cystic fibrosis airway epithelial cells
AU Fajac, Isabelle; Briand, Pascale; **Monsigny, Michel**; **Midoux, Patrick**
CS INSERM U380, ICGM, Universite Rene Descartes (Paris V), Paris, 75014, Fr.
SO Hum. Gene Ther. (1999), 10(3), 395-406
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal
LA English
AB We have examd. the membrane lectin expressed by immortalized normal and cystic fibrosis (CF) airway epithelial cells, using fluorescein-labeled neoglycoproteins; the uptake of plasmid DNA using fluoresceinylated glycoplexes (plasmid/glycosylated polylysine **complexes**); and the efficiency of gene transfer when glycosylated polylysines and glycosylated, partially gluconoylated polylysines were used as vectors. The most efficient uptake of neoglycoproteins by normal and CF cells was obtained with mannosylated BSA (bovine serum albumin). Similarly, the most efficient uptake of plasmid DNA was obtained with glycoplexes bearing .alpha.-D-Man residues. Surprisingly, glycoplexes bearing .alpha.-D-Man residues were poorly efficient for gene transfer into normal and CF cells. The highest luciferase activity was achieved with lactosylated polylysine- and .beta.-D-GlcNAc-substituted gluconoylated polylysine as vectors. Gene transfer efficiency obtained with gluconoylated polylysine bearing .beta.-D-GlcNAc residues was similar to that obsd. with polyethylenimine (PEI; 25 and 800 kDa) and 10-fold higher than that obsd. with lipofectin and **LipofectAMINE**. These results suggest that the transfection efficiency with glycoplexes is not detd. only by the specificity of the lectin expressed at the cell surface membrane but also by intracellular trafficking of the glycoplexes, which could be mediated by lectins present inside the cells.
IT **492-61-5D**, .beta.-D-Glucose, deriv. with polylysine
492-62-6D, .alpha.-D-Glucose, deriv. with polylysine
5965-66-2D, .beta.-D-Lactose, deriv. with polylysine
6014-42-2D, .alpha.-L-Rhamnose, deriv. with polylysine
6696-41-9D, .alpha.-L-Fucose, deriv. with polylysine
7296-15-3D, .alpha.-D-Mannose, deriv. with polylysine
14131-60-3D, N-Acetyl-.beta.-D-**galactosamine**, deriv. with polylysine **14131-68-1D**, N-Acetyl-.beta.-D-**glucosamine**, deriv. with polylysine **14215-68-0D**, N-Acetyl-.alpha.-D-**galactosamine**, deriv. with polylysine **25104-18-1D**, Polylysine, glycosylated **38000-06-5D**, Polylysine, glycosylated
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sugar-mediated uptake of glycosylated polylysines and gene transfer into normal and cystic fibrosis airway epithelial cells)
RN 492-61-5 HCAPLUS
CN .beta.-D-Glucopyranose (9CI) (CA INDEX NAME)

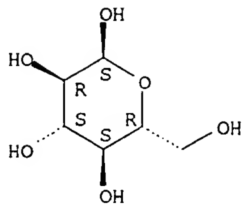
Absolute stereochemistry. Rotation (+).



RN 492-62-6 HCAPLUS

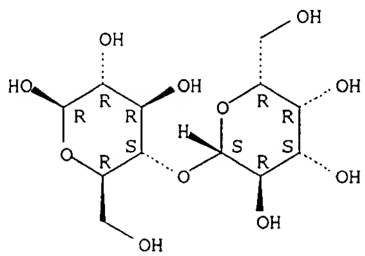
CN .alpha.-D-Glucopyranose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



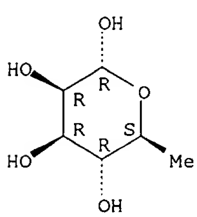
RN 5965-66-2 HCAPLUS
CN .beta.-D-Glucopyranose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



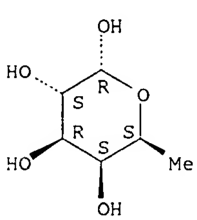
RN 6014-42-2 HCAPLUS
CN .alpha.-L-Mannopyranose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



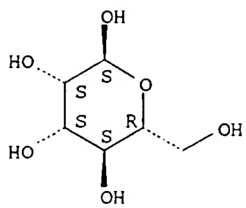
RN 6696-41-9 HCAPLUS
CN .alpha.-L-Galactopyranose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



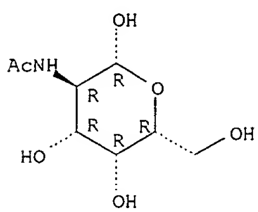
RN 7296-15-3 HCAPLUS
CN .alpha.-D-Mannopyranose (9CI) (CA INDEX NAME)

Absolute stereochemistry.



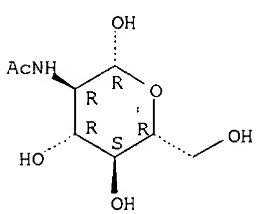
RN 14131-60-3 HCAPLUS
CN .beta.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



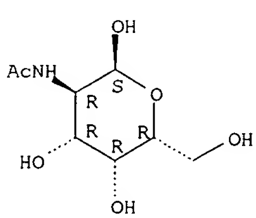
RN 14131-68-1 HCAPLUS
CN .beta.-D-Glucopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 14215-68-0 HCAPLUS
CN .alpha.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

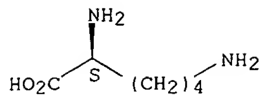


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

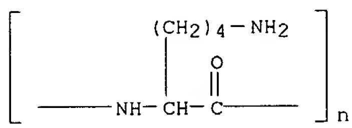
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



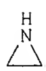
RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



IT **9002-98-6**, Polyethylenimine **128835-92-7**, Lipofectin **158571-62-1**, **LipofectAMINE**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sugar-mediated uptake of glycosylated polylysines and gene transfer into normal and cystic fibrosis airway epithelial cells: comparison with other uptake enhancers)
RN 9002-98-6 HCAPLUS
CN Aziridine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 151-56-4
CMF C2 H5 N

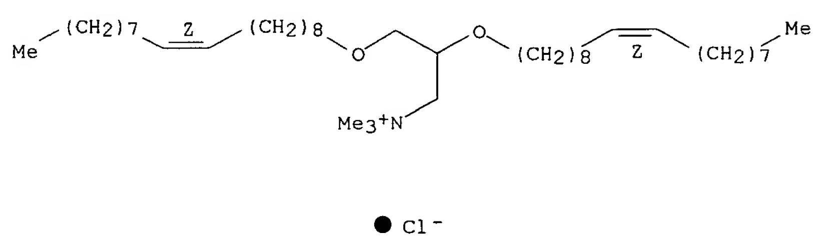


RN 128835-92-7 HCAPLUS
CN 1-Propanaminium, N,N,N-trimethyl-2,3-bis[(9Z)-9-octadecenyloxy]-, chloride, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 104162-48-3
CMF C42 H84 N O2 . Cl
CDES 2:Z,Z

Double bond geometry as shown.

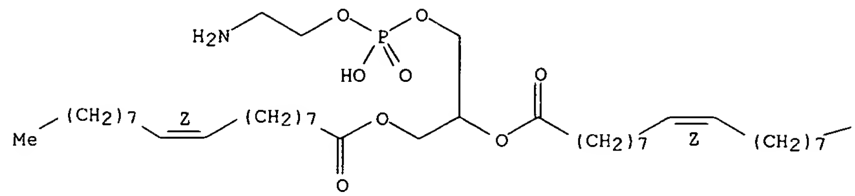


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



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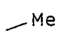


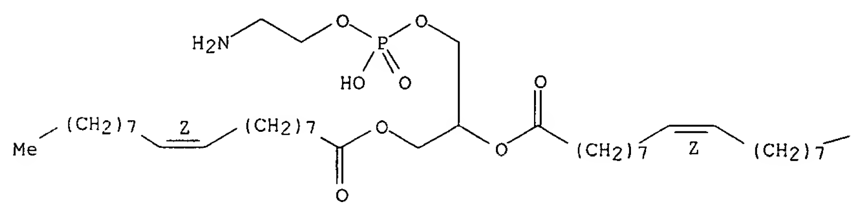
RN 158571-62-1 HCAPLUS
CN 1-Propanaminium, N-[3-[[3-[[4-[(3-aminopropyl)amino]butyl]amino]propyl]amino]-3-oxopropyl]-N,N-dimethyl-2,3-bis[[(9Z)-1-oxo-9-octadecenyl]oxy]-, salt with trifluoroacetic acid (1:1), mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



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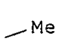


CM 2

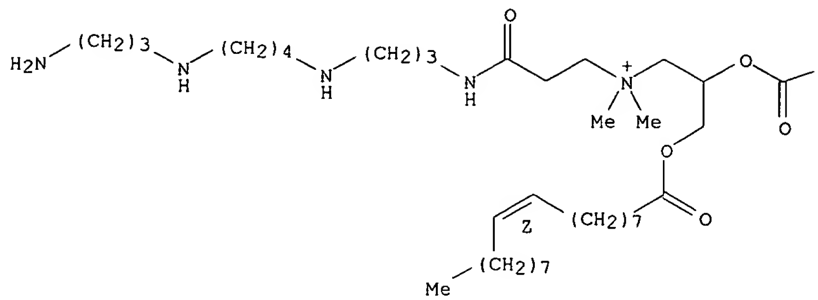
CRN 185097-43-2
CMF C54 H106 N5 O5 . C2 F3 O2

CM 3

CRN 181508-68-9
CMF C54 H106 N5 O5
CDES 2:Z,Z

Double bond geometry as shown.

PAGE 1-A



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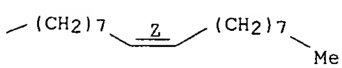
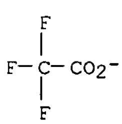


CM 4

CRN 14477-72-6
CMF C2 F3 O2



RE.CNT 31

RE
(1) Barasch, J; Nature (London) 1991, V352, P70 HCAPLUS
(2) Biwersi, J; Proc Natl Acad Sci U S A 1996, V93, P12484 HCAPLUS
(3) Boussif, O; Proc Natl Acad Sci U S A 1995, V92, P7297 HCAPLUS
(4) Bradbury, N; Science 1992, V256, P530 HCAPLUS
(5) Cozens, A; Am J Respir Cell Mol Biol 1994, V10, P38 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d bib abs hitstr l10 6

L10  ANSWER 6 OF 18  HCAPLUS  COPYRIGHT 2000 ACS
AN   1998:352961  HCAPLUS
DN   129:37202
TI   Novel polymeric complexes for the transfection of nucleic acids,
     with residues causing the destabilization of cell membranes
IN   Midoux, Patrick; Monsigny, Michel
PA   I.D.M. Immuno-Designed Molecules, Fr.; Midoux, Patrick; Monsigny, Michel
SO   PCT Int. Appl., 83 pp.
     CODEN: PIXXD2
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
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PI   WO 9822610        A1   19980528       WO 1997-FR2022   19971110
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             DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
             US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     FR 2755976        A1   19980522       FR 1996-13990    19961115
     FR 2755976        B1   19990115
     AU 9851239        A1   19980610       AU 1998-51239    19971110
     EP 946744         A1   19991006       EP 1997-945903   19971110
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRAI FR 1996-13990     19961115
     WO 1997-FR2022    19971110
OS   MARPAT 129:37202
AB   The invention concerns a complex between at least a (neg.
     charged) nucleic acid and at least a pos. charged polymeric conjugate, the
     bond between the nucleic acid and the polymeric conjugate being
     electrostatic in nature, the polymeric conjugate contg. a polymer formed
     by monomer units bearing free NH3+ functions, and being such that: the
     free NH3+ functions of said monomer units are substituted in a ratio of
     .gtoreq.10 % by residues causing in weak acid medium destabilization of
     cell membranes, in particular the endocytosis vesicle membrane, and/or
     endosomes; said residues having further the following properties: they
     comprise a functional group for being fixed to said polymer, they are not
     active as recognition signal identified by a cell membrane receptor, they
     can comprise at least one free NH3+ function; said uncharged residues
     having further the following properties: they comprise at least a hydroxyl
     group, they are not active as recognition signal identified by a cell
     membrane receptor, the hydroxyl groups of said uncharged residues being
     capable of being substituted by at least a mol. which constitutes a
     recognition signal identified by a cell membrane receptor, with
     reservation that the whole set of free NH3+ functions is at least 30 % of
     the no. of monomer units of the polymeric network of said polymeric
     conjugate.
IT   9002-06-6, Thymidine kinase
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (gene encoding, of Herpes simplex virus; polymeric complexes
        for the transfection of nucleic acids, with residues causing the
        destabilization of cell membranes)
RN   9002-06-6  HCAPLUS
CN   Kinase (phosphorylating), thymidine (9CI)  (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT   9001-28-9, Factor ix 9014-00-0, Luciferase
     9025-05-2, Cytosine deaminase 9026-93-1, Adenosine
     deaminase 9029-73-6, Phenylalanine hydroxylase 9031-11-2
     , .beta.-Galactosidase 9036-22-0, Tyrosine hydroxylase
     9040-07-7, Chloramphenicol acetyl transferase 113189-02-9
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, Factor viii
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene encoding; polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 9001-28-9 HCAPLUS
CN Blood-coagulation factor IX (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9014-00-0 HCAPLUS
CN Luciferase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9025-05-2 HCAPLUS
CN Deaminase, cytosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9026-93-1 HCAPLUS
CN Deaminase, adenosine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9029-73-6 HCAPLUS
CN Oxygenase, phenylalanine 4-mono- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9031-11-2 HCAPLUS
CN Galactosidase, .beta.- (9CI) (CA INDEX NAME)

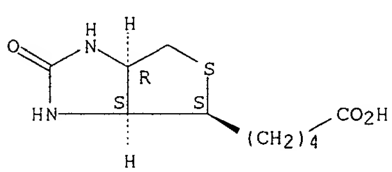
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9036-22-0 HCAPLUS
CN Oxygenase, tyrosine 3-mono- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9040-07-7 HCAPLUS
CN Acetyltransferase, chloramphenicol (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 113189-02-9 HCAPLUS
CN Blood-coagulation factor VIII, procoagulant (9CI) (CA INDEX NAME)

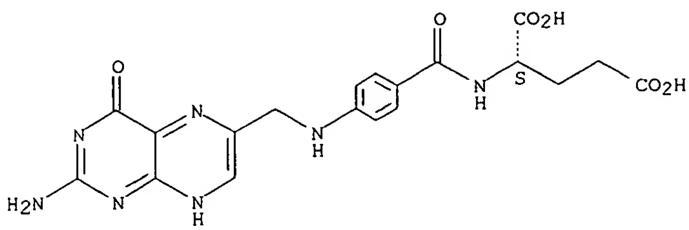
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **58-85-5**, Biotin **59-30-3**, Folic acid, biological studies
135-16-0
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 58-85-5 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



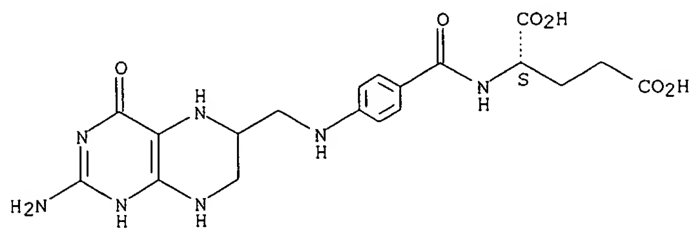
RN 59-30-3 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 135-16-0 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

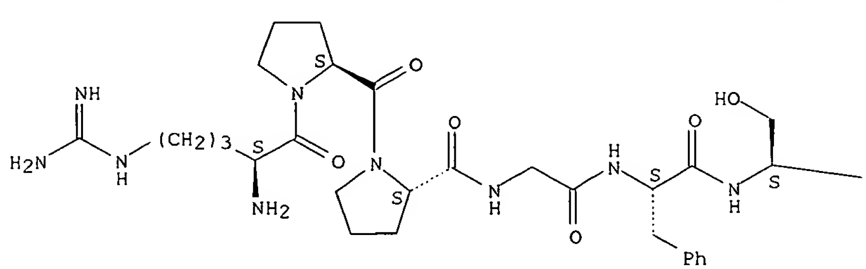
Absolute stereochemistry.



IT **58-82-2**, Bradykinin **37213-49-3**, .alpha.-MSH **37221-79-7**, Vip **40077-57-4** **59880-97-6** **77036-51-2** **82867-73-0** **82867-74-1** **85637-73-6**, ANP **85985-42-8** **91917-63-4**, Atrial natriuretic peptide-28 (human reduced) **118850-72-9** **140913-62-8** **208337-46-6** **208337-47-7** **208342-23-8** **208342-24-9**
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 58-82-2 HCAPLUS
CN Bradykinin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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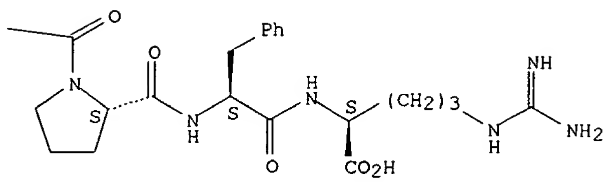


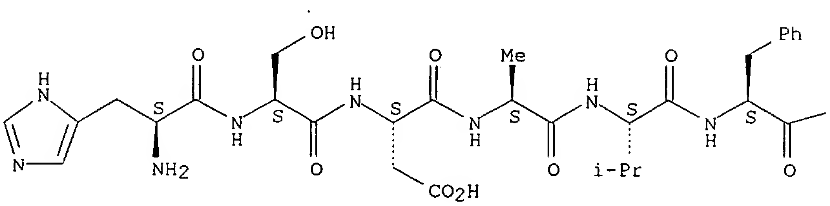
RN 37213-49-3 HCAPLUS
CN .alpha.-Melanotropin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 37221-79-7 HCAPLUS
CN Vasoactive intestinal polypeptide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 40077-57-4 HCAPLUS
CN Vasoactive intestinal octacosapeptide (swine) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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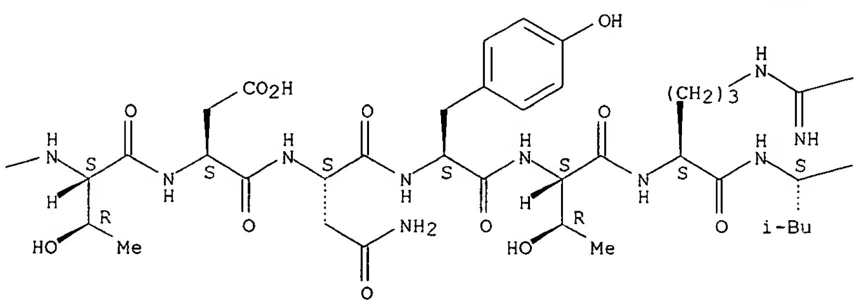

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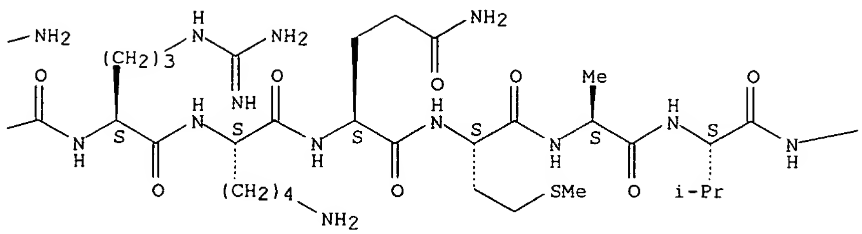

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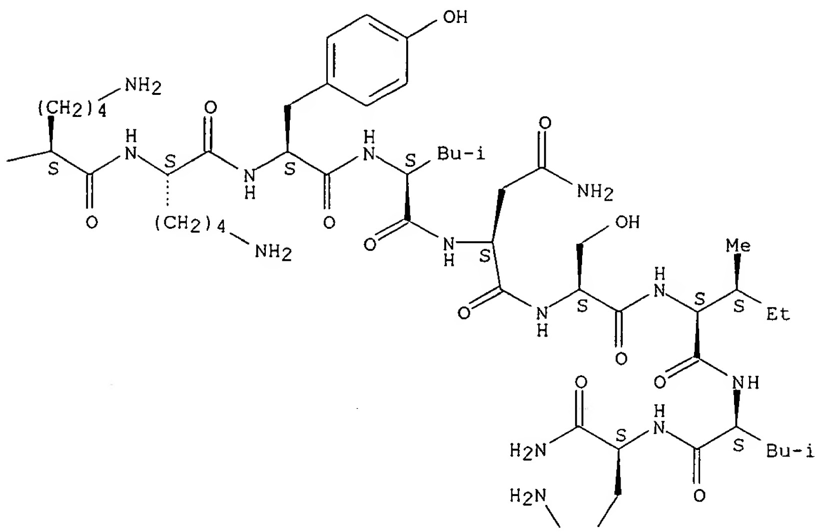

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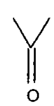
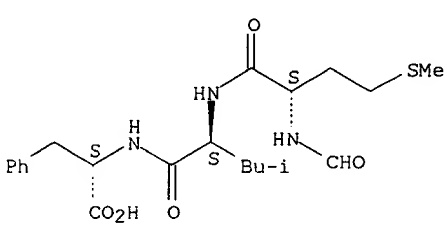


RN 59880-97-6 HCAPLUS
CN L-Phenylalanine, N-formyl-L-methionyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

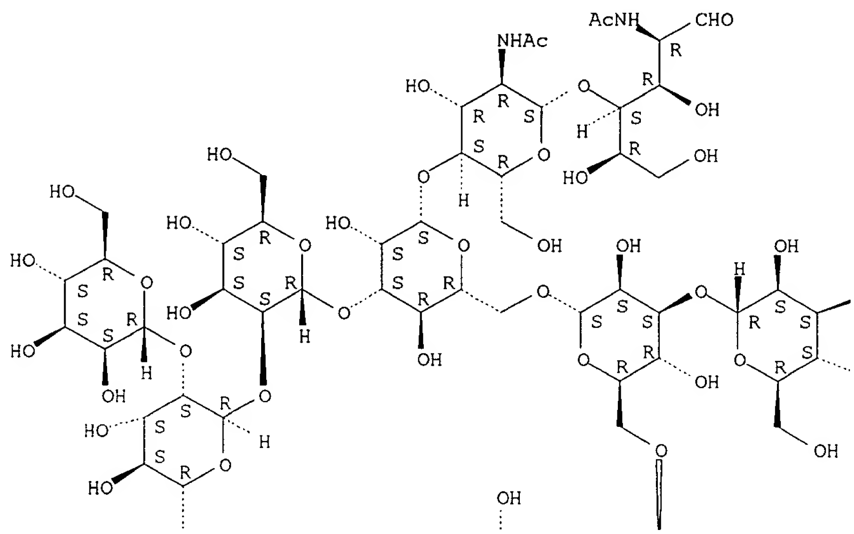


RN 77036-51-2 HCAPLUS

CN D-Glucose, O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.6)-O-[O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.3)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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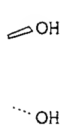

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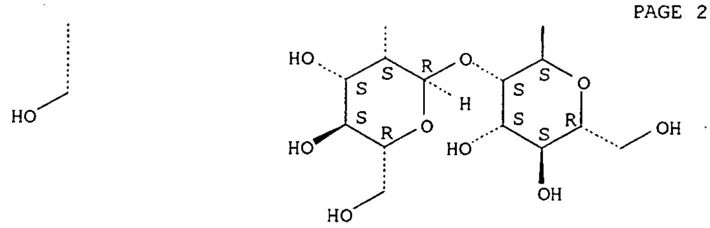
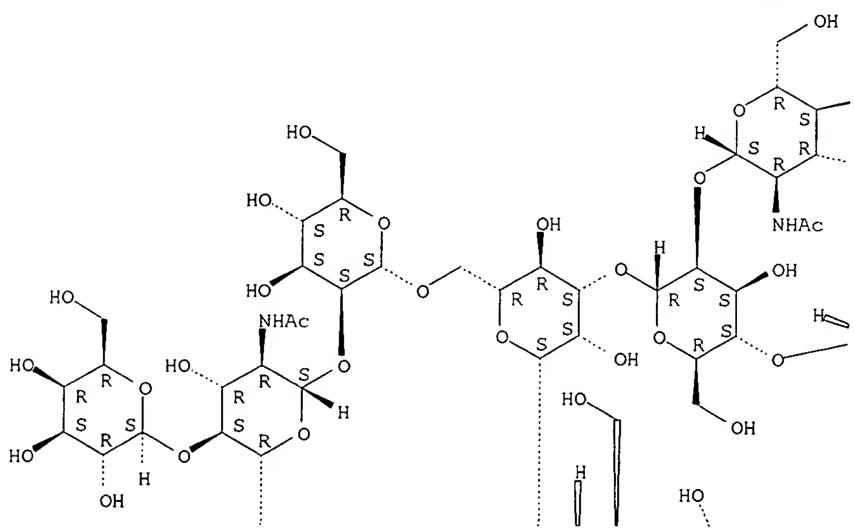


RN 82867-73-0 HCAPLUS
CN D-Glucose, O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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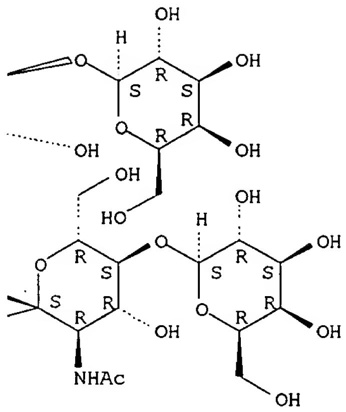

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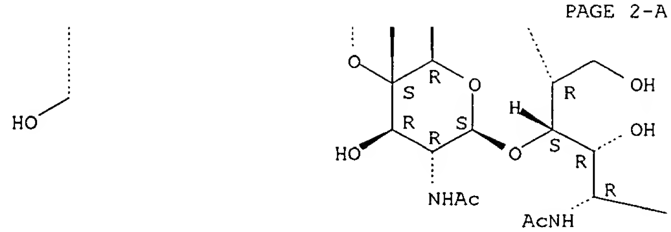

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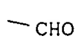
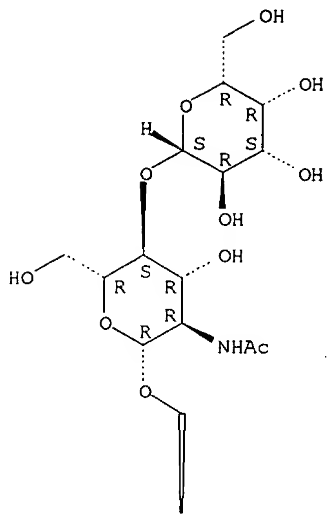


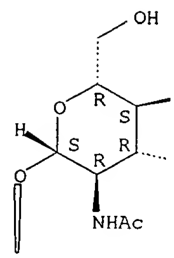
RN 82867-74-1 HCAPLUS

CN D-Glucose, O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-O-[O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.6)]-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

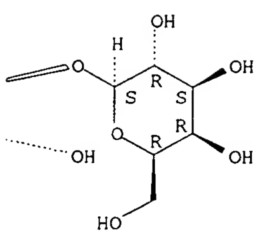
Absolute stereochemistry.

PAGE 1-A





PAGE 1-B



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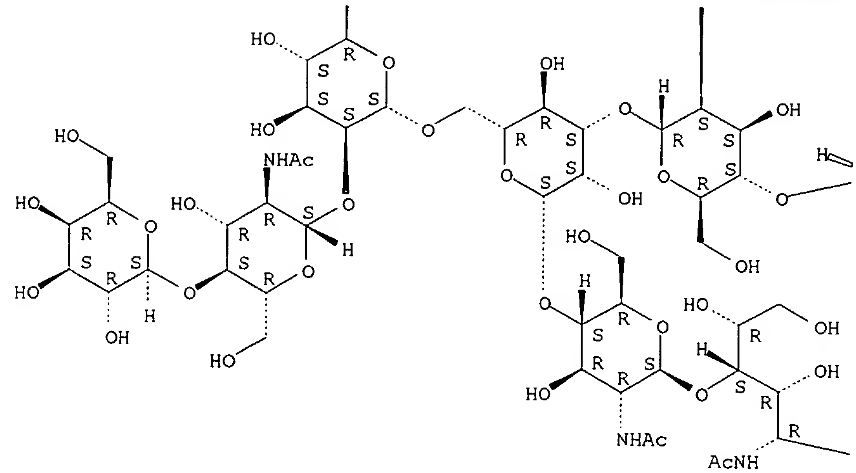
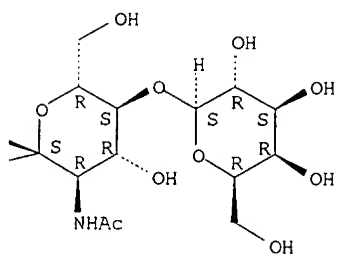
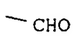


PAGE 2-B

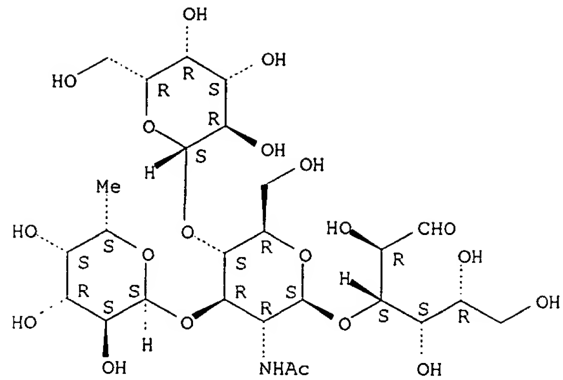




RN 85637-73-6 HCAPLUS
CN Atrial natriuretic peptide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 85985-42-8 HCAPLUS
CN D-Galactose, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.3)-O-[.beta.-D-galactopyranosyl-(1.fwdarw.4)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)- (9CI) (CA INDEX NAME)

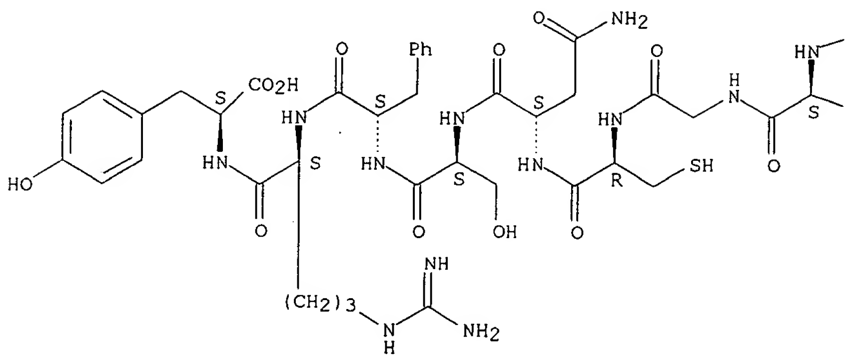
Absolute stereochemistry.



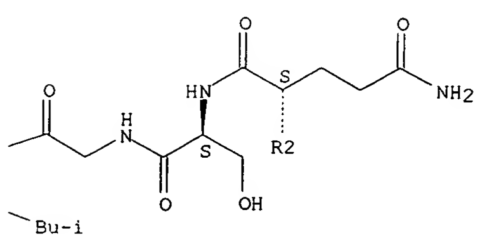
RN 91917-63-4 HCAPLUS
CN Atrial natriuretic peptide-28 (human reduced) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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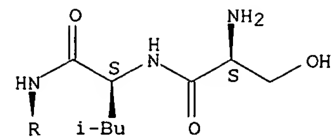
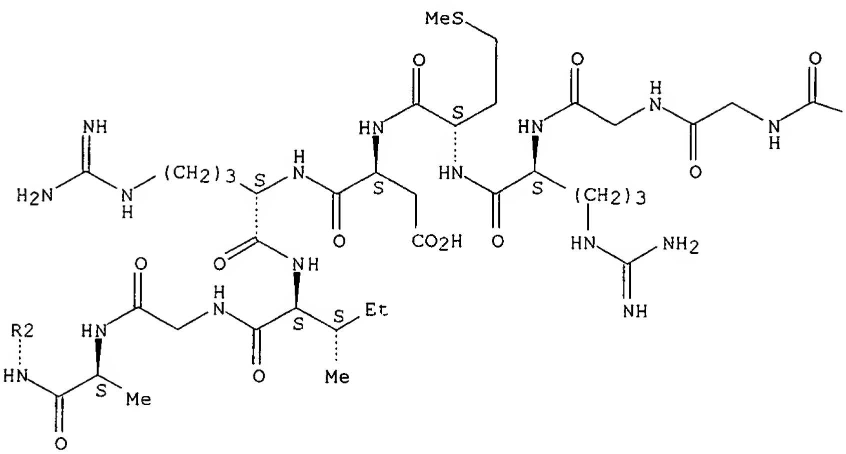
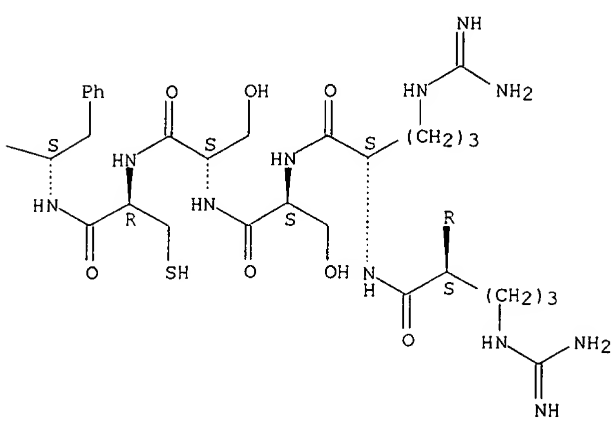


PAGE 3-A



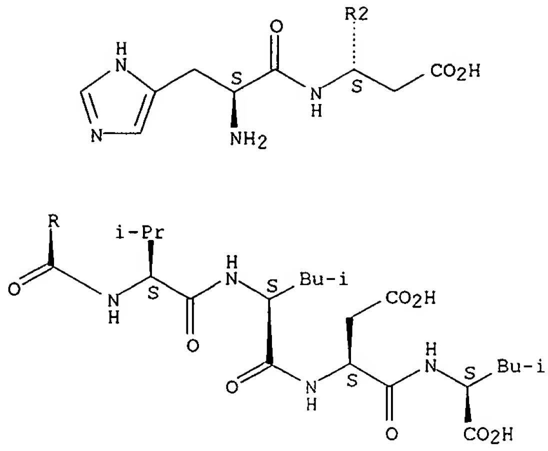
PAGE 3-B



RN 118850-72-9 HCAPLUS
CN L-Leucine, L-histidyl-L-.alpha.-aspartyl-L-methionyl-L-asparaginyl-L-lysyl-L-valyl-L-leucyl-L-.alpha.-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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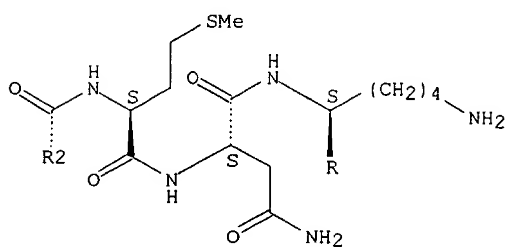
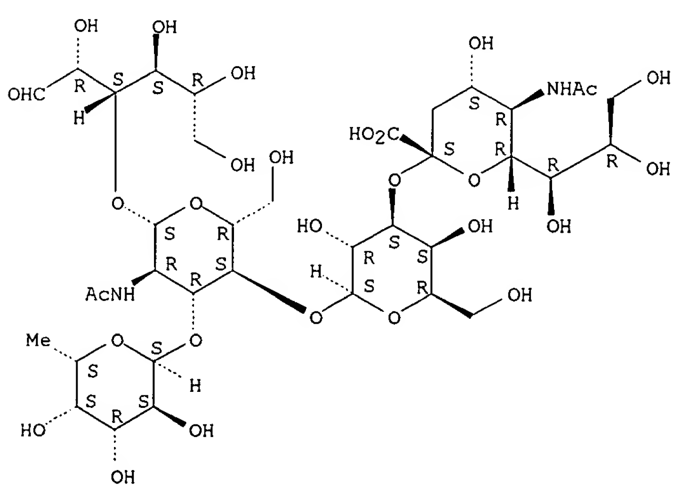


RN 140913-62-8 HCAPLUS
CN D-Galactose, O-(N-acetyl-.alpha.-neuraminosyl)-(2.fwdarw.3)-O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-O-[6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.3)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)- (9CI) (CA INDEX NAME)

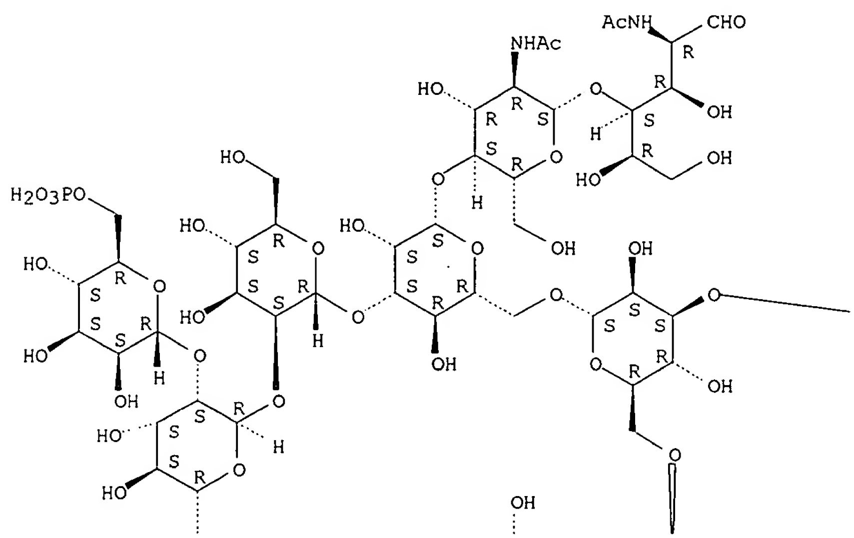
Absolute stereochemistry.



RN 208337-46-6 HCAPLUS
CN D-Glucose, O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-6-O-phosphono-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.6)-O-[O-6-O-phosphono-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.3)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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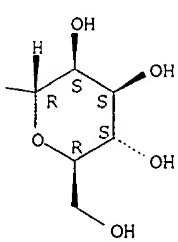

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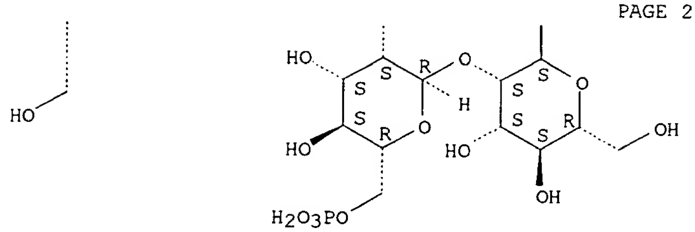
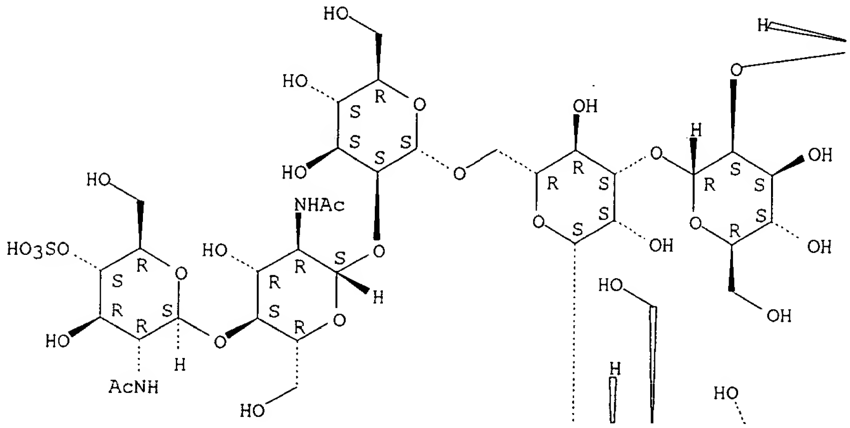


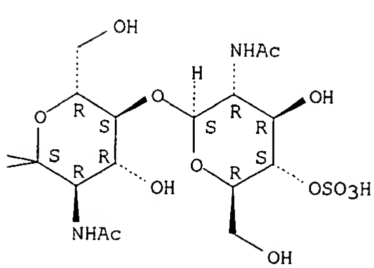
RN 208337-47-7 HCAPLUS
CN D-Glucose, O-2-(acetylamino)-2-deoxy-4-O-sulfo-.beta.-D-glucopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-2-(acetylamino)-2-deoxy-4-O-sulfo-.beta.-D-glucopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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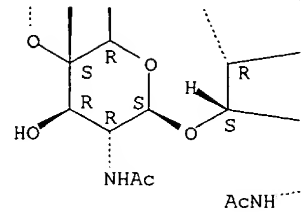

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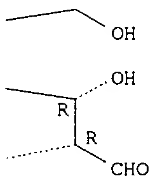
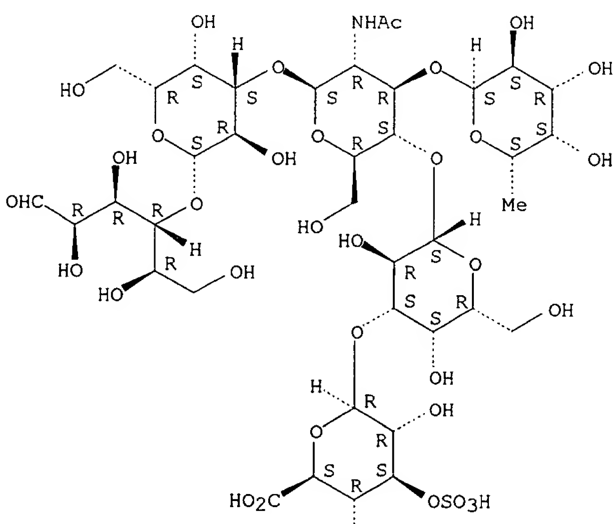


RN 208342-23-8 HCAPLUS
CN D-Glucose, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.3)-O-[O-3-O-sulfo-.beta.-D-glucopyranuronosyl-(1.fwdarw.3)-.beta.-D-galactopyranosyl-(1.fwdarw.4)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)-O-.beta.-D-galactopyranosyl-(1.fwdarw.4)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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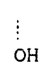
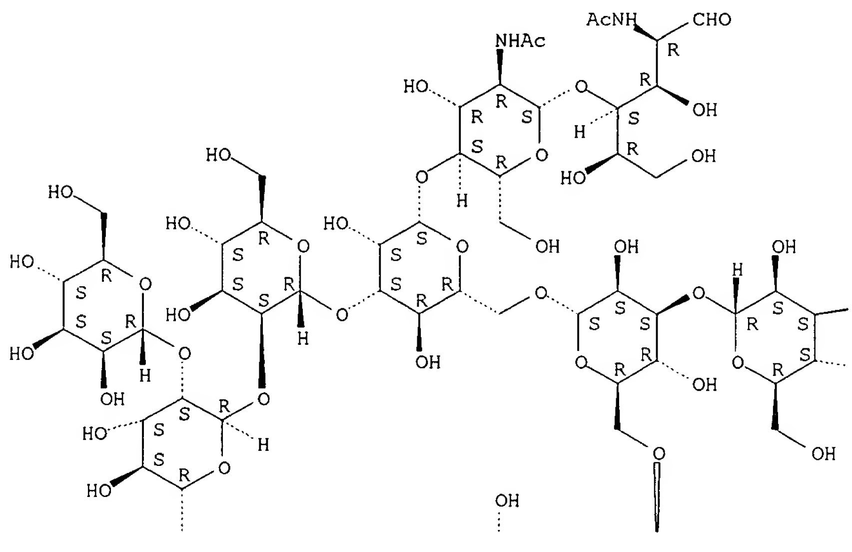


RN 208342-24-9 HCAPLUS

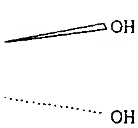
CN D-Glucose, O-.alpha.-D-mannopyranosyl-(1.fwdarw.3)-O-[O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-6-O-phosphono-.alpha.-D-mannopyranosyl-(1.fwdarw.6)]-O-.alpha.-D-mannopyranosyl-(1.fwdarw.6)-O-[O-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-O-6-O-phosphono-.alpha.-D-mannopyranosyl-(1.fwdarw.2)-.alpha.-D-mannopyranosyl-(1.fwdarw.3)]-O-.beta.-D-mannopyranosyl-(1.fwdarw.4)-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.4)-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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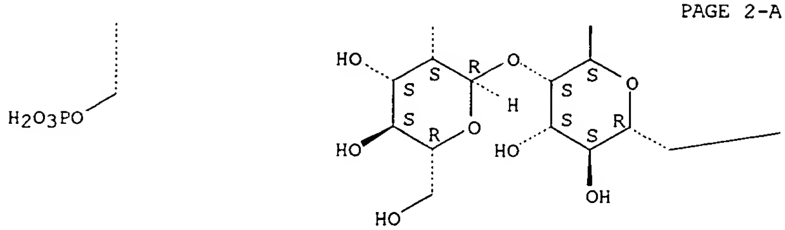

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—OPO_3H_2

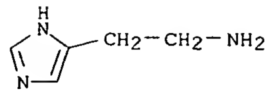
IT 1404-04-2, Neomycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 1404-04-2 HCAPLUS
CN Neomycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

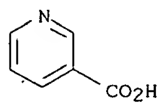
IT **14798-03-9**, Ammonium ion, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 14798-03-9 HCAPLUS
CN Ammonium (8CI, 9CI) (CA INDEX NAME)

NH_4^+

IT **51-45-6, Histamine**, biological studies **59-67-6**, Nicotinic acid, biological studies **70-26-8**, Ornithine **71-00-1, Histidine**, biological studies **86-68-0**, Quininic acid **89-00-9**, Quinolinic acid **90-34-6**, Primaquine **91-22-5D**, Quinoline, derivs. **110-86-1D**, Pyridine, derivs. **119-24-4**, Pteroic acid **288-32-4D**, **Imidazole**, derivs. **305-84-0**, Carnosine **501-75-7** **526-95-4D**, Gluconic acid, derivs. **644-42-8** **645-65-8**, 1H-**Imidazole**-4-acetic acid **2236-60-4D**, Pterin, derivs. **2466-76-4**, Acetyl **imidazole** **4298-14-0 7212-31-9 9041-92-3**, .alpha.1-Antitrypsin **9061-61-4**, Nerve growth factor **14403-45-3 16042-25-4**, 1H-**Imidazole**-2-carboxylic acid **25104-18-1**, Polylysine **26469-60-3**, Quinoline carboxylic acid **28095-60-5 38000-06-5**, Polylysine
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 51-45-6 HCAPLUS
CN 1H-Imidazole-4-ethanamine (9CI) (CA INDEX NAME)

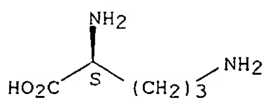


RN 59-67-6 HCAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



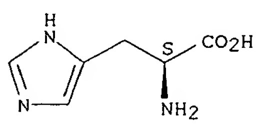
RN 70-26-8 HCAPLUS
CN L-Ornithine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

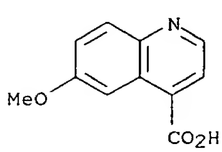


RN 71-00-1 HCAPLUS
CN L-Histidine (9CI) (CA INDEX NAME)

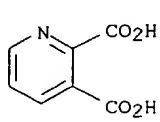
Absolute stereochemistry. Rotation (-).



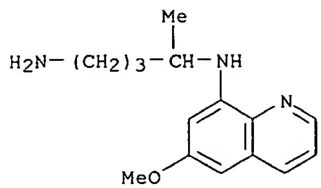
RN 86-68-0 HCAPLUS
CN 4-Quinolinecarboxylic acid, 6-methoxy- (9CI) (CA INDEX NAME)



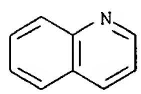
RN 89-00-9 HCAPLUS
CN 2,3-Pyridinedicarboxylic acid (8CI, 9CI) (CA INDEX NAME)



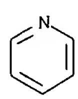
RN 90-34-6 HCAPLUS
CN 1,4-Pentanediamine, N4-(6-methoxy-8-quinolinyl)- (9CI) (CA INDEX NAME)



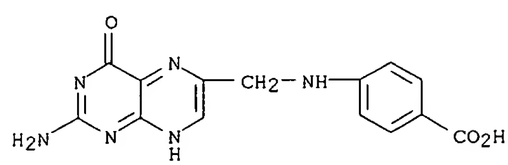
RN 91-22-5 HCAPLUS
CN Quinoline (8CI, 9CI) (CA INDEX NAME)



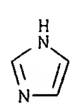
RN 110-86-1 HCAPLUS
CN Pyridine (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 119-24-4 HCAPLUS
CN Benzoic acid, 4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]- (9CI) (CA INDEX NAME)

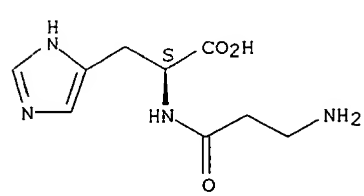


RN 288-32-4 HCAPLUS
CN 1H-Imidazole (9CI) (CA INDEX NAME)

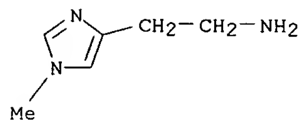


RN 305-84-0 HCAPLUS
CN L-Histidine, .beta.-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

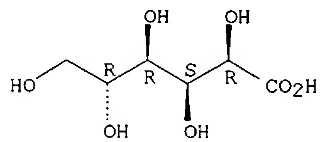


RN 501-75-7 HCAPLUS
CN 1H-Imidazole-4-ethanamine, 1-methyl- (9CI) (CA INDEX NAME)

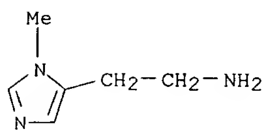


RN 526-95-4 HCAPLUS
CN D-Gluconic acid (9CI) (CA INDEX NAME)

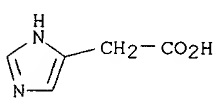
Absolute stereochemistry.



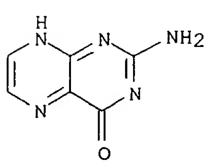
RN 644-42-8 HCAPLUS
CN 1H-Imidazole-5-ethanamine, 1-methyl- (9CI) (CA INDEX NAME)



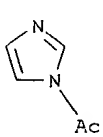
RN 645-65-8 HCAPLUS
CN 1H-Imidazole-4-acetic acid (9CI) (CA INDEX NAME)



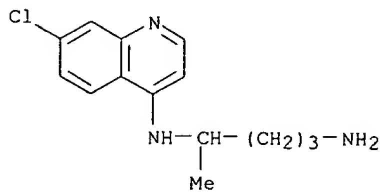
RN 2236-60-4 HCAPLUS
CN 4(1H)-Pteridinone, 2-amino- (8CI, 9CI) (CA INDEX NAME)



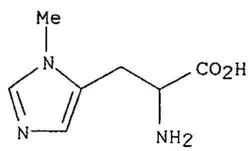
RN 2466-76-4 HCAPLUS
CN 1H-Imidazole, 1-acetyl- (9CI) (CA INDEX NAME)



RN 4298-14-0 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)- (9CI) (CA INDEX NAME)



RN 7212-31-9 HCAPLUS
CN Histidine, 3-methyl- (9CI) (CA INDEX NAME)

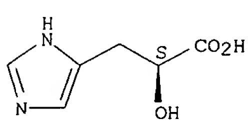


RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, .alpha.1- (9CI) (CA INDEX NAME)

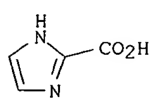
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9061-61-4 HCAPLUS
CN Nerve growth factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 14403-45-3 HCAPLUS
CN 1H-Imidazole-4-propanoic acid, .alpha.-hydroxy-, (.alpha.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 16042-25-4 HCAPLUS
CN 1H-Imidazole-2-carboxylic acid (9CI) (CA INDEX NAME)

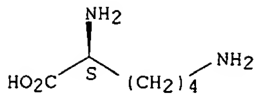


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

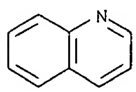
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.

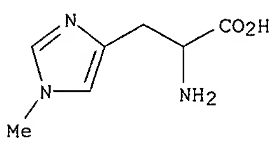


RN 26469-60-3 HCAPLUS
CN Quinolinecarboxylic acid (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

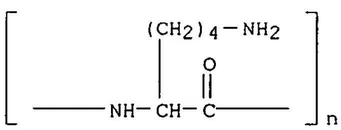


D1—CO2H

RN 28095-60-5 HCAPLUS
CN Histidine, 1-methyl- (9CI) (CA INDEX NAME)



RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



IT **25988-63-0P**, Polylysine hydrobromide
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 25988-63-0 HCAPLUS
CN L-Lysine, homopolymer, hydrobromide (9CI) (CA INDEX NAME)

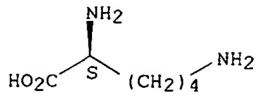
CM 1

CRN 25104-18-1
CMF (C6 H14 N2 O2)x
CCI PMS

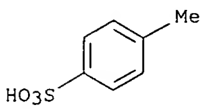
CM 2

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

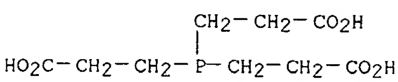
Absolute stereochemistry.



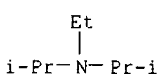
IT **104-15-4**, reactions **5961-85-3**, Tris-
carboxyethylphosphine **7087-68-5, Diisopropylethylamine**
20866-46-0 56602-33-6 112241-19-7
208342-20-5
RL: RCT (Reactant)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 104-15-4 HCAPLUS
CN Benzenesulfonic acid, 4-methyl- (9CI) (CA INDEX NAME)



RN 5961-85-3 HCAPLUS
CN Propanoic acid, 3,3',3''-phosphinidynetris- (9CI) (CA INDEX NAME)

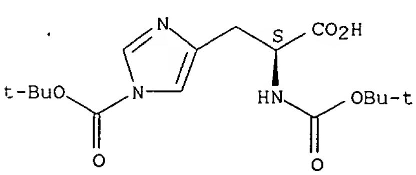


RN 7087-68-5 HCAPLUS
CN 2-Propanamine, N-ethyl-N-(1-methylethyl)- (9CI) (CA INDEX NAME)



RN 20866-46-0 HCAPLUS
CN L-Histidine, N,1-bis[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

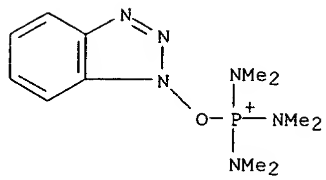
Absolute stereochemistry.



RN 56602-33-6 HCAPLUS
CN Phosphorus(1+), (1-hydroxy-1H-benzotriazolato-O)tris(N-methylmethanaminato)-, (T-4)-, hexafluorophosphate(1-) (9CI) (CA INDEX NAME)

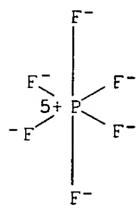
CM 1

CRN 56602-32-5
CMF C12 H22 N6 O P
CDES 7:T-4



CM 2

CRN 16919-18-9
CMF F6 P
CCI CCS



RN 112241-19-7 HCAPLUS
CN 2,5-Pyrrolidinedione, 1-[[4-[1-(2-pyridinyldithio)ethyl]benzoyl]oxy]- (9CI) (CA INDEX NAME)

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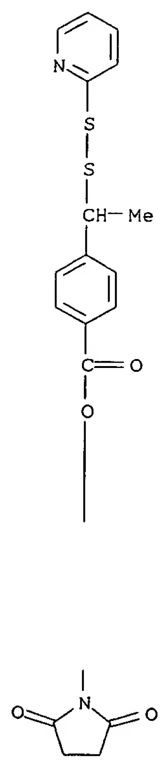
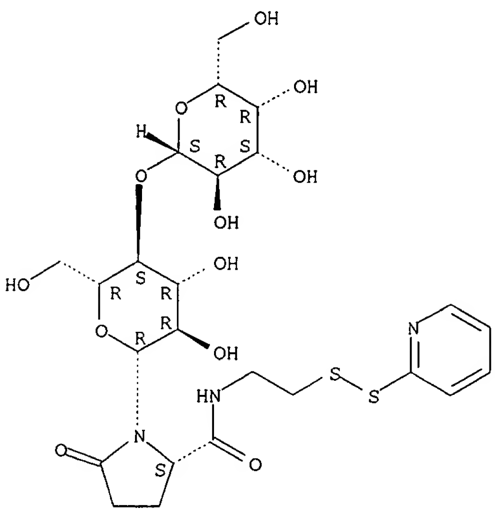


RN 208342-20-5 HCAPLUS
CN 2-Pyrrolidinecarboxamide, 1-(4-O-.beta.-D-galactopyranosyl-.beta.-D-glucopyranosyl)-5-oxo-N-[2-(2-pyridinyldithio)ethyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

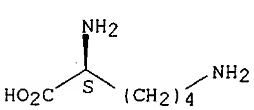


IT **25104-18-1DP**, Polylysine, reaction products with 4-carbonyl-.alpha.-methyl-.alpha.-(2-pyridinyldithio)toluene N-hydroxysuccinimide **208342-19-2P** **208342-21-6P** **208342-22-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

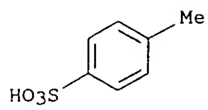
Absolute stereochemistry.



RN 208342-19-2 HCAPLUS
CN L-Lysine, homopolymer, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 104-15-4
CMF C7 H8 O3 S



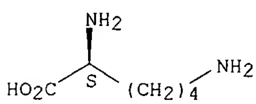
CM 2

CRN 25104-18-1
CMF (C6 H14 N2 O2)x
CCI PMS

CM 3

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

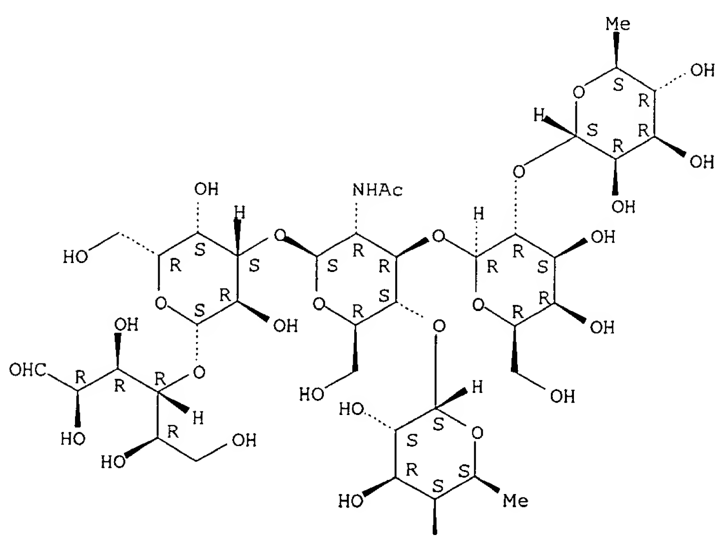
Absolute stereochemistry.



RN 208342-21-6 HCAPLUS
CN D-Glucose, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.4)-O-[O-6-deoxy-.alpha.-L-mannopyranosyl-(1.fwdarw.2)-.beta.-D-galactopyranosyl-(1.fwdarw.3)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)-O-.beta.-D-galactopyranosyl-(1.fwdarw.4)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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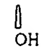
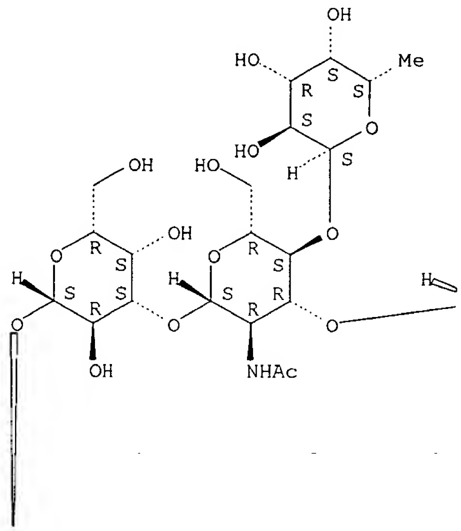


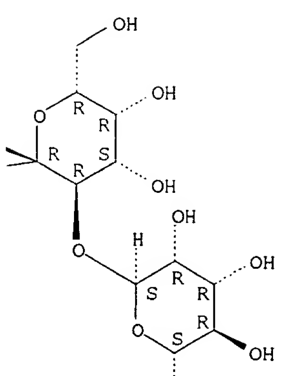
RN 208342-22-7 HCAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[O-6-deoxy-.alpha.-D-galactopyranosyl-(1.fwdarw.4)-O-[O-6-deoxy-.alpha.-L-mannopyranosyl-(1.fwdarw.2)-.beta.-D-galactopyranosyl-(1.fwdarw.3)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)-O-.beta.-D-galactopyranosyl-(1.fwdarw.4)-.beta.-D-glucopyranosyl]-5-oxo-N-[2-(2-pyridinyldithio)ethyl]-, (2S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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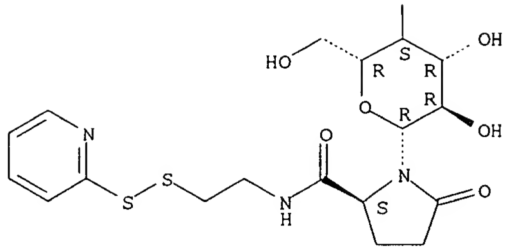

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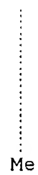
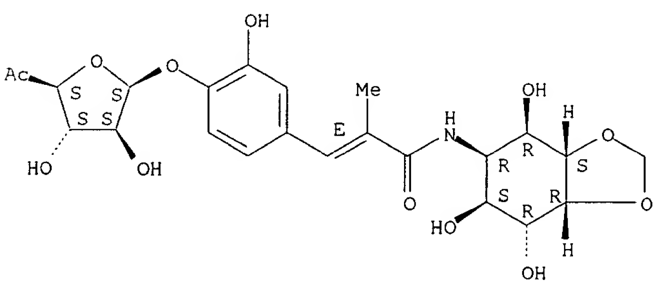


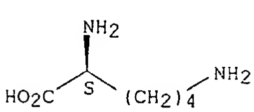
IT **6379-56-2,** Hygromycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(resistance to; polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 6379-56-2 HCAPLUS
CN D-neo-Inositol, 5-deoxy-5-[[(2E)-3-[4-[(6-deoxy-.beta.-D-arabino-hexofuranos-5-ulos-1-yl)oxy]-3-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-1,2-O-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

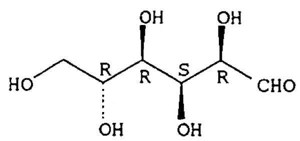


IT **56-87-1,** L-Lysine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.epsilon.-amino group of; polymeric **complexes** for the transfection of nucleic acids, with residues causing the destabilization of cell membranes)
RN 56-87-1 HCAPLUS
CN L-Lysine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

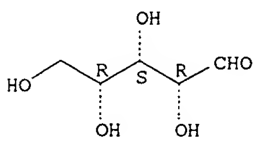


Absolute stereochemistry.



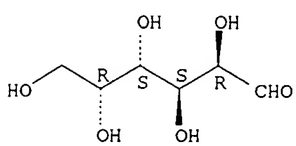
RN 58-86-6 HCAPLUS
CN D-Xylose (9CI) (CA INDEX NAME)

Absolute stereochemistry.



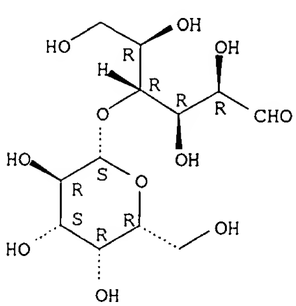
RN 59-23-4 HCAPLUS
CN D-Galactose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



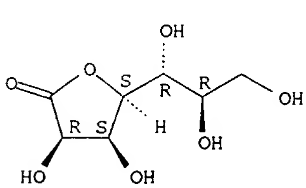
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



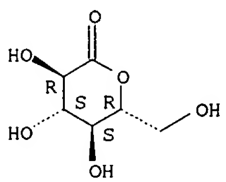
RN 89-67-8 HCAPLUS
CN D-glycero-D-gulo-Heptonic acid, .gamma.-lactone (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



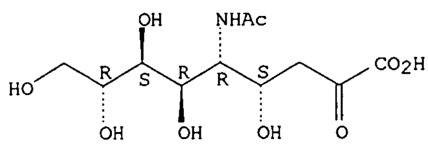
RN 90-80-2 HCAPLUS
CN D-Gluconic acid, .delta.-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.



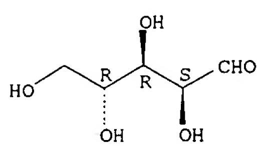
RN 131-48-6 HCAPLUS
CN Neuraminic acid, N-acetyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

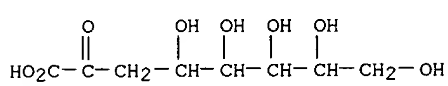


RN 147-81-9 HCAPLUS
CN Arabinose (8CI, 9CI) (CA INDEX NAME)

Relative stereochemistry.

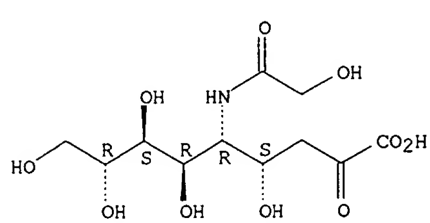


RN 1069-03-0 HCAPLUS
CN 2-Octulosonic acid, 3-deoxy- (9CI) (CA INDEX NAME)



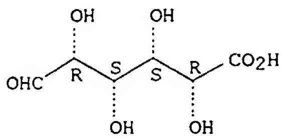
RN 1113-83-3 HCAPLUS
CN Neuraminic acid, N-(hydroxyacetyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



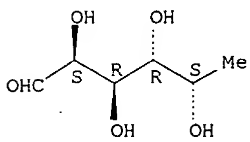
RN 2073-35-0 HCAPLUS
CN L-Iduronic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



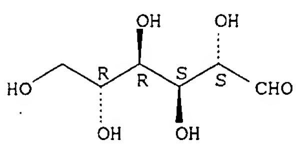
RN 2438-80-4 HCAPLUS
CN L-Galactose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



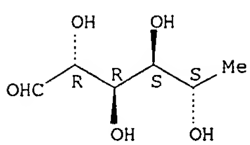
RN 3458-28-4 HCAPLUS
CN D-Mannose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



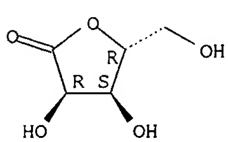
RN 3615-41-6 HCAPLUS
CN L-Mannose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



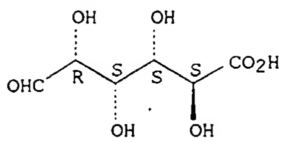
RN 5336-08-3 HCAPLUS
CN D-Ribonic acid, .gamma.-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 6556-12-3 HCAPLUS
CN D-Glucuronic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.

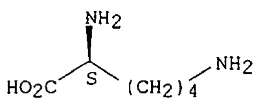


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

CM 1

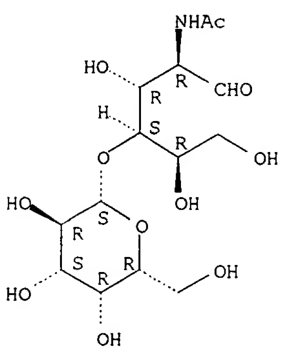
CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.

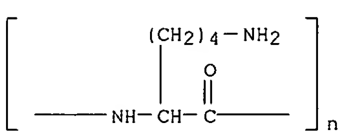


RN 32181-59-2 HCAPLUS
CN D-Glucose, 2-(acetylamino)-2-deoxy-4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

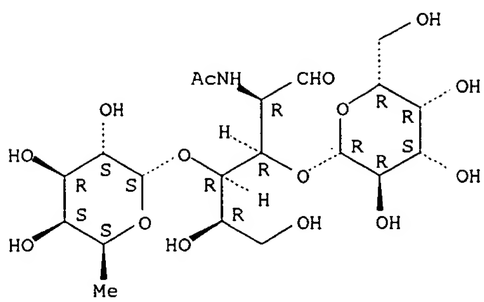


RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



RN 56570-03-7 HCAPLUS
CN D-Glucose, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.4)-O-[.beta.-D-galactopyranosyl-(1.fwdarw.3)]-2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



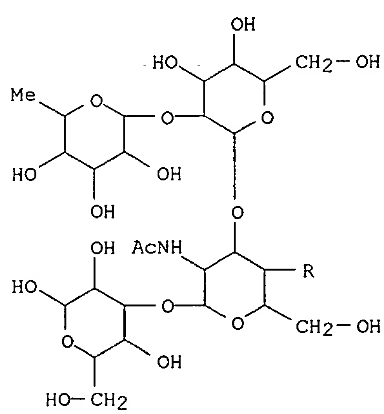
RN 85637-73-6 HCAPLUS
CN Atrial natriuretic peptide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 117660-12-5 HCAPLUS
CN Hexitol, O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.4)-O-[O-6-deoxy-.alpha.-L-galactopyranosyl-(1.fwdarw.2)-.beta.-D-galactopyranosyl-(1.fwdarw.3)]-O-2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl-(1.fwdarw.3)-O-D-galactopyranosyl-(1.fwdarw.?)- (9CI) (CA INDEX NAME)

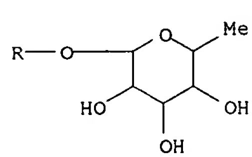
CM 1

CRN 117660-11-4
CMF C32 H55 N O24
CDES *

PAGE 1-A

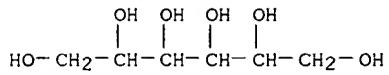


PAGE 2-A



CM 2

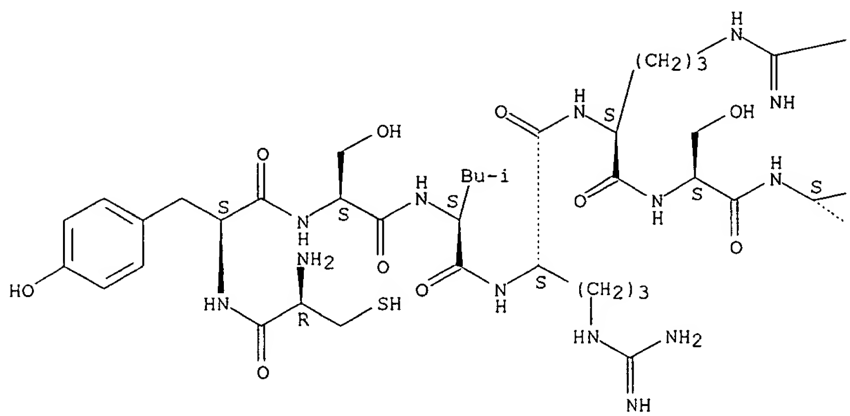
CRN 45007-61-2
CMF C6 H14 O6



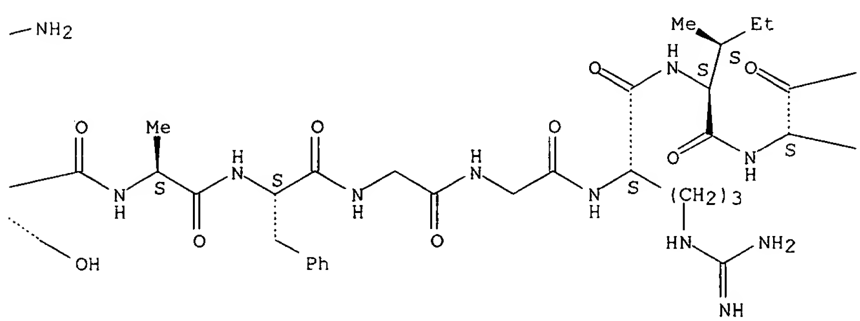
RN 205534-18-5 HCAPLUS
CN 1-20-Atrial natriuretic peptide-28 (rat reduced), N-(L-cysteinyl-L-tyrosyl)-7-L-alanine-20-L-alanine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

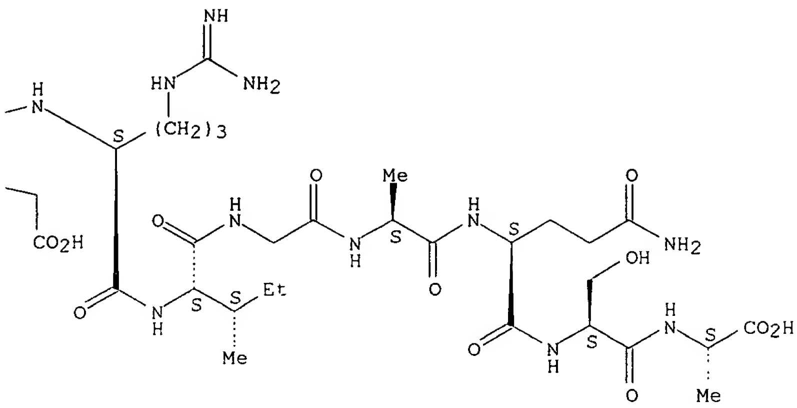
PAGE 1-A



PAGE 1-B



PAGE 1-C



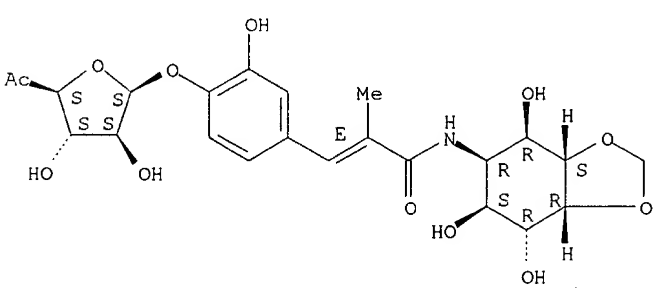
IT **1404-04-2,** Neomycin **6379-56-2,** Hygromycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression of gene for resistance to; **complexes** of nucleic acid and polylysine conjugated with non-charged residues and recognition signals for the transfection of cells)

RN 1404-04-2 HCAPLUS
CN Neomycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 6379-56-2 HCAPLUS
CN D-neo-Inositol, 5-deoxy-5-[[(2E)-3-[4-[(6-deoxy-.beta.-D-arabino-hexofuranos-5-ulos-1-yl)oxy]-3-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-1,2-O-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **9002-06-6,** Thymidine kinase **9014-00-0,** Luciferase **9031-11-2,** .beta.-Galactosidase **9040-07-7,** Chloramphenicol acetyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression of gene for; **complexes** of nucleic acid and polylysine conjugated with non-charged residues and recognition signals for the transfection of cells)

RN 9002-06-6 HCAPLUS
CN Kinase (phosphorylating), thymidine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9014-00-0 HCAPLUS
CN Luciferase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9031-11-2 HCAPLUS
CN Galactosidase, .beta.- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9040-07-7 HCAPLUS
CN Acetyltransferase, chloramphenicol (9CI) (CA INDEX NAME)

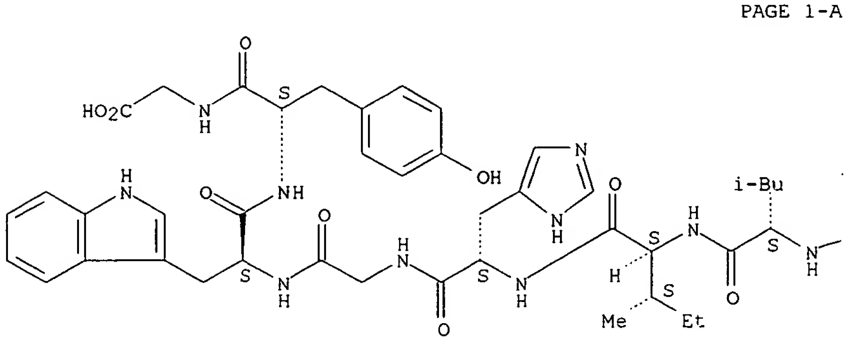
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d bib abs hitstr 110 8

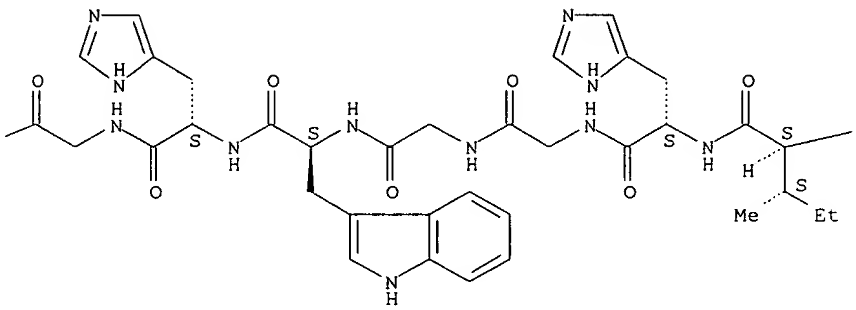
L10 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:127047 HCAPLUS
DN 128:221609
TI Membrane Permeabilization and Efficient Gene Transfer by a Peptide Containing Several **Histidines**
AU **Midoux, Patrick**; Kichler, Antoine; Boutin, Valerie; Maurizot, Jean-Claude; **Monsigny, Michel**
CS Centre de Biophysique Moleculaire, CNRS et Universite d'Orleans, Orleans, F-47071, Fr.
SO Bioconjugate Chem. (1998), 9(2), 260-267
CODEN: BCCHES; ISSN: 1043-1802
PB American Chemical Society
DT Journal
LA English
AB We designed a peptide, H5WYG (GLFHAIAHFIHGGWHGLIHGWYG), that permeabilizes cell membrane at a slightly acidic pH but not at neutral pH. Absorbance, fluorescence, and CD spectra showed that H5WYG undergoes a dramatic conformational change between pH 7.0 and 6.0 that correlates with the protonation of the histidyl residues. Cell permeabilization studies monitored by flow cytometry on living cells showed that H5WYG permeabilizes the cell membrane with a great efficiency at pH 6.4 but was not active at neutral pH; at pH 6.8, the peptide permeabilized 50% of the cells at 20 .degree.C in 10 min. H5WYG increased the expression of genes transferred to cells as glycosylated polylysine-DNA **complexes**, and the transfection efficiency was not impaired in the presence of serum. Therefore, this peptide contg. several **histidines** that become pos. charged when the pH decreased to less than 7.0 is a suitable helper for delivering mols. into the cytosol upon either permeabilization of the plasma membrane induced by lowering the extracellular medium to pH 6.4 or permeabilization of the endosomal membrane induced by acidification of endosomes.
IT **204448-87-3**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(membrane permeabilization and efficient gene transfer by peptide contg. several **histidines**)
RN 204448-87-3 HCAPLUS
CN Glycine, glycyl-L-leucyl-L-phenylalanyl-L-histidyl-L-alanyl-L-isoleucyl-L-alanyl-L-histidyl-L-phenylalanyl-L-isoleucyl-L-histidylglycylglycyl-L-tryptophyl-L-histidylglycyl-L-leucyl-L-isoleucyl-L-histidylglycyl-L-tryptophyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

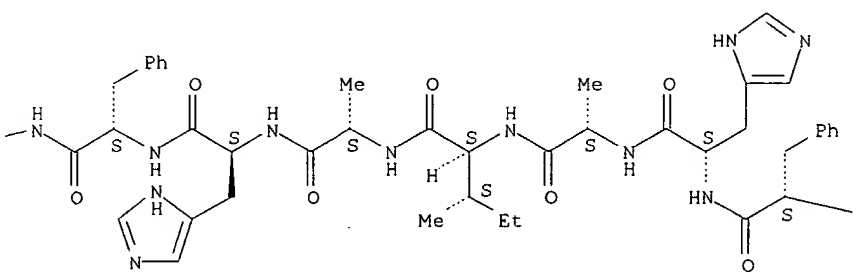
PAGE 1-A



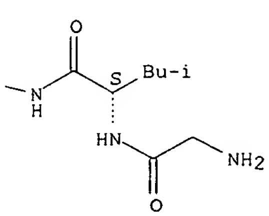
PAGE 1-B



PAGE 1-C



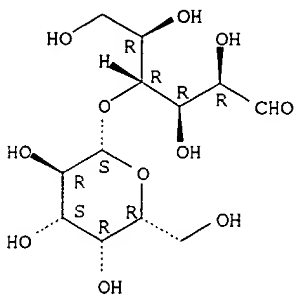
PAGE 1-D



IT **63-42-3D**, Lactose, reaction products with polylysine, DNA
complexes
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(membrane permeabilization and efficient gene transfer by peptide

contg. several **histidines**)
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

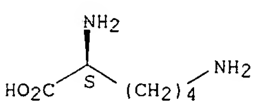


IT **25104-18-1D**, Polylysine, lactosylated, DNA **complexes**
38000-06-5D, Polylysine, lactosylated, DNA **complexes**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(transfection of; membrane permeabilization and efficient gene transfer by peptide contg. several **histidines**)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

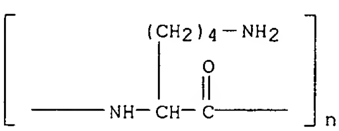
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



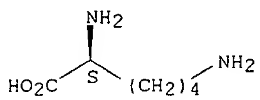
RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)

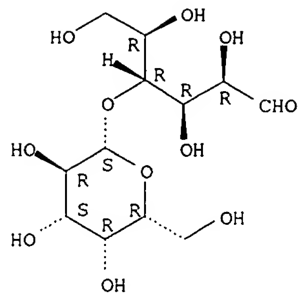


CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

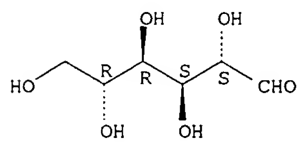
Absolute stereochemistry.





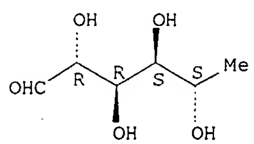
RN 3458-28-4 HCAPLUS
CN D-Mannose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



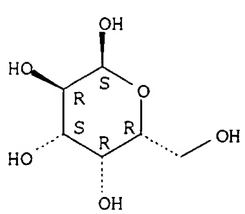
RN 3615-41-6 HCAPLUS
CN L-Mannose, 6-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



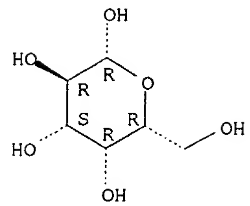
RN 3646-73-9 HCAPLUS
CN .alpha.-D-Galactopyranose (9CI) (CA INDEX NAME)

Absolute stereochemistry.



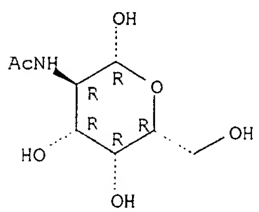
RN 7296-64-2 HCAPLUS
CN .beta.-D-Galactopyranose (9CI) (CA INDEX NAME)

Absolute stereochemistry.



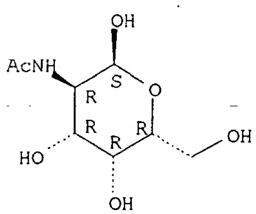
RN 14131-60-3 HCAPLUS
CN .beta.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 14215-68-0 HCAPLUS
CN .alpha.-D-Galactopyranose, 2-(acetylamino)-2-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

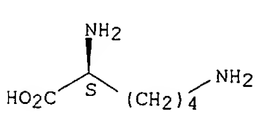


IT **25104-18-1D**, Polylysine, gluconoylated and glycosylated derivs.
38000-06-5D, Polylysine, gluconoylated and glycosylated derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gluconoylated and glycosylated polylysines as vectors for gene transfer into cystic fibrosis airway epithelial cells)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

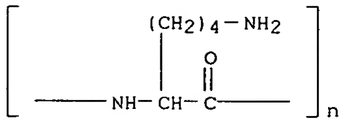
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

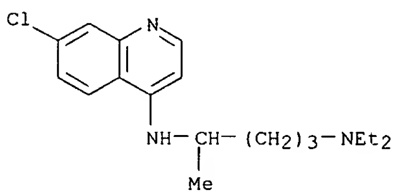
Absolute stereochemistry.



RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



IT **54-05-7**, Chloroquine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in glycosidated polylysine-dependent transformation of airway epithelium; gluconoylated and glycosylated polylysines as vectors for gene transfer into cystic fibrosis airway epithelial cells)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)



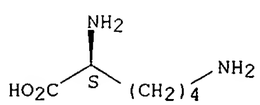
=> d bib abs hitstr l10 11

L10 ANSWER 11 OF 18 HCAPLUS
AN 1996:423937 HCAPLUS
DN 125:133841
TI Selective transfection of animal cells by nonviral vectors, polylysine carrying recognition signals
AU **Monsigny, Michel; Midoux, Patrick;** Roche, Annie-Claude; Legrand, Alain; Mayer, Roger
CS Cent. Biophysique Moleculaire, CNRS, Orleans, 45071, Fr.
SO C. R. Seances Soc. Biol. Ses Fil. (1996), 190(1), 39-43
CODEN: CRSBAW; ISSN: 0037-9026
DT Journal
LA French
AB A process for the selective transfer of genes using glycosylated polylysine was established. Glycosylated polylysines and plasmid DNA form **complexes** which are taken up be cells expressing surface lectins recognizing the sugar moieties of glycosylated polylysines. Modifications made to this process allow for efficient and specific transfer in in vitro animal cell models.
IT **25104-18-1,** Polylysine **38000-06-5,** Polylysine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective transfer of genes using glycosylated polylysines)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

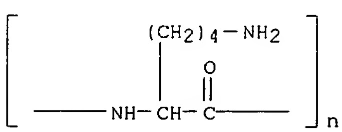
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.

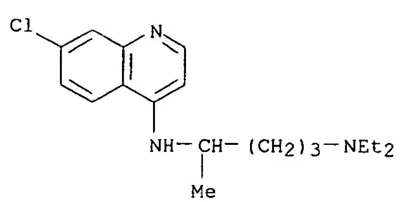


RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX NAME)



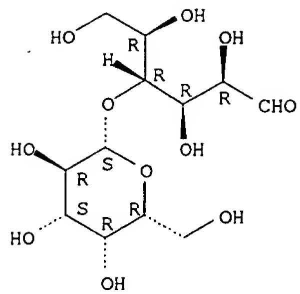
=> d bib abs hitstr l10 12

L10 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:317957 HCAPLUS
DN 125:27149
TI Putative role of chloroquine in gene transfer into a human hepatoma cell line by DNA/lactosylated polylysine **complexes**
AU Erbacher, Patrick; Roche, Annie Claude; **Monsigny, Michel; Midoux, Patrick**
CS Centre Biophysique Moleculaire, CNRS Univ. d'Orleans, Orleans, F-45071, Fr.
SO Exp. Cell Res. (1996), 225(1), 186-194
CODEN: ECREAL; ISSN: 0014-4827
DT Journal
LA English
AB Chloroquine improves drastically the transfection of cells upon exposure to plasmid DNA/glycosylated polylysine **complexes**. So far the mechanism of action of chloroquine is not well understood. In this paper, the effect of chloroquine was investigated by measuring the transfection efficiency of a human hepatocarcinoma (HepG2 cells) by pSV2LUC/lactosylated polylysine **complexes** involving their internalization via the galactose-specific membrane lectin of these cells. The luciferase activity in the transfected cells was maximal when the transfection was performed for 3 or 4 h in the presence of 100 .mu.M chloroquine. The luciferase activity was also enhanced in the presence of primaquine, a chloroquine analog, but was not increased when transfection was performed in the presence of ammonium chloride, **methylamine**, spermine, or monensin, compds. known to neutralize the pH of the endocytotic vesicle lumen as chloroquine does. Chloroquine enters cells and accumulates in vesicular compartments; the overall intracellular concn. increases to 9 mM, which means that in the vesicular compartment, the chloroquine concns. is still higher. At such high concns., chloroquine induces the dissocn. of plasmid DNA/lactosylated polylysine **complexes**, as shown in a cellular expts.
IT **54-05-7**, Chloroquine **63-42-3D**, polylysine substituted with **25104-18-1D**, Polylysine, lactosylated derivs.
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(chloroquine in gene transfer into human hepatoma cell line by DNA/lactosylated polylysine **complexes**)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)



RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

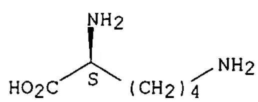


RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

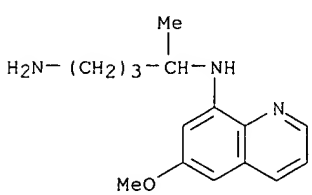
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



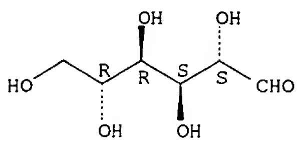
IT **90-34-6**, Primaquine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(chloroquine in gene transfer into human hepatoma cell line by DNA/lactosylated polylysine **complexes** in relation to effect of primaquine)
RN 90-34-6 HCAPLUS
CN 1,4-Pentanediamine, N4-(6-methoxy-8-quinolinyl)- (9CI) (CA INDEX NAME)



Polylysine, glycosylated **83869-56-1**, Granulocyte-macrophage
colony-simulating factor **128835-92-7**, Lipofectin
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological
study); PROC (Process); USES (Uses)
(gene transfer by DNA/glycosylated polylysine **complexes** into
human blood monocyte-derived macrophages)

RN 3458-28-4 HCAPLUS
CN D-Mannose (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 9015-73-0 HCAPLUS
CN Dextran, 2-(diethylamino)ethyl ether (9CI) (CA INDEX NAME)

CM 1

CRN 9004-54-0
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-37-8
CMF C6 H15 N O

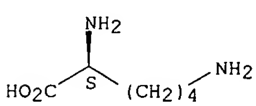
$Et_2N-CH_2-CH_2-OH$

RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

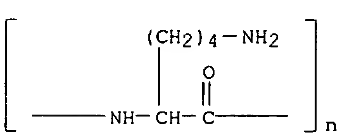
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.



RN 38000-06-5 HCAPLUS
CN Poly[imino[(1S)-1-(4-aminobutyl)-2-oxo-1,2-ethanediyl]] (9CI) (CA INDEX
NAME)



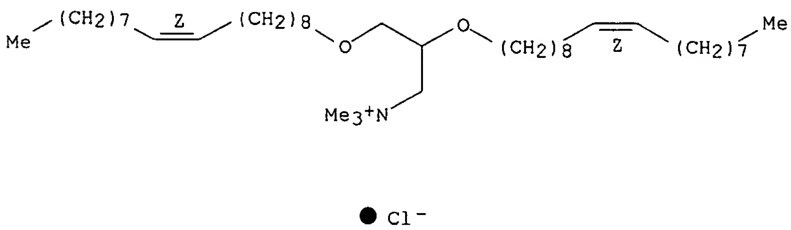
RN 83869-56-1 HCAPLUS
CN Colony-stimulating factor 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 128835-92-7 HCAPLUS
CN 1-Propanaminium, N,N,N-trimethyl-2,3-bis[(9Z)-9-octadecenyloxy]-, chloride, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 104162-48-3
CMF C42 H84 N O2 . Cl
CDES 2:Z,Z

Double bond geometry as shown.

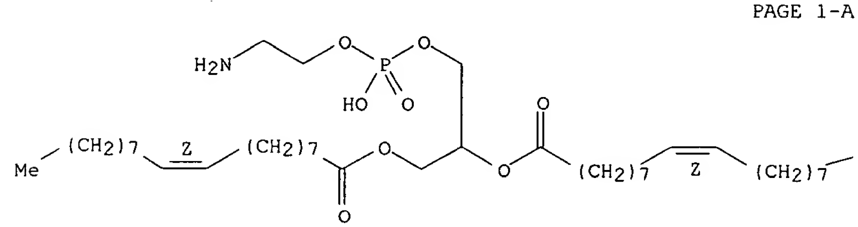


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



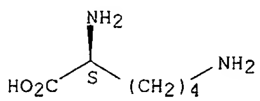
PAGE 1-B

complexes in relation to size and sugar substitution level of glycosylated polylysines and plasmid size)
RN 25104-18-1 HCAPLUS
CN L-Lysine, homopolymer (9CI) (CA INDEX NAME)

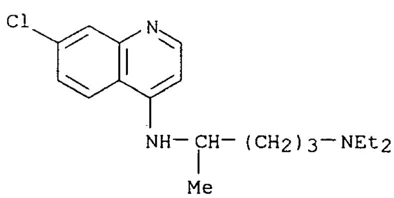
CM 1

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

Absolute stereochemistry.

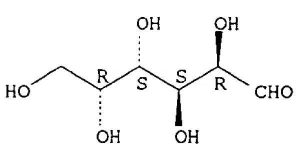


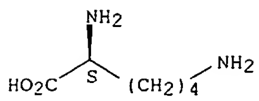
IT **54-05-7**, Chloroquine **59-23-4**, Galactose, biological studies
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(human hepatoma (HepG2) cells which express a galactose-specific membrane lectin are efficiently transfected in the presence of chloroquine with pSV2Luc plasmid **complexed** with a lactosylated polylysine)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)



RN 59-23-4 HCAPLUS
CN D-Galactose (9CI) (CA INDEX NAME)

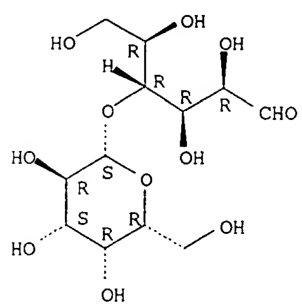
Absolute stereochemistry. Rotation (+).



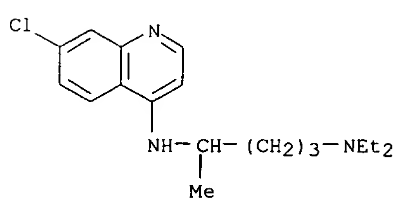


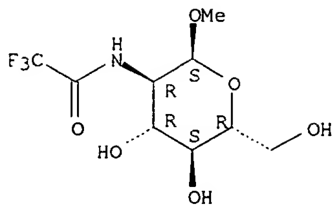
IT 63-42-3, Lactose
RL: BIOL (Biological study)
(polylysine substituted with, in **complexes** with plasmid, transformation of HepG2 cells with, by receptor-mediated endocytosis)
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



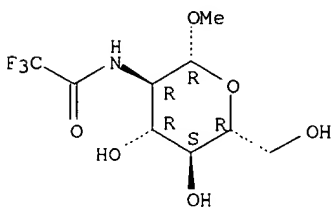
IT 54-05-7, Chloroquine
RL: BIOL (Biological study)
(transformation of HepG2 cells with plasmid DNA/glycosylated polylysine **complexes** enhancement by, receptor-mediated endocytosis in relation to)
RN 54-05-7 HCAPLUS
CN 1,4-Pentanediamine, N4-(7-chloro-4-quinolinyl)-N1,N1-diethyl- (9CI) (CA INDEX NAME)





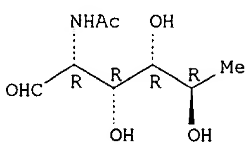
RN 40299-08-9 HCAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[(trifluoroacetyl)amino]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



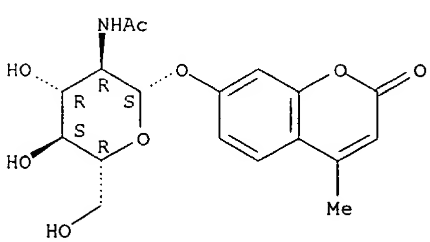
RN 40614-71-9 HCAPLUS
CN D-Glucose, 2-(acetylamino)-2,6-dideoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **37067-30-4**
RL: BIOL (Biological study)
(monosaccharides binding to wheat germ agglutinin study by fluorescence spectroscopy in relation to)
RN 37067-30-4 HCAPLUS
CN 2H-1-Benzopyran-2-one, 7-[[2-(acetylamino)-2-deoxy-.beta.-D-glucopyranosyl]oxy]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

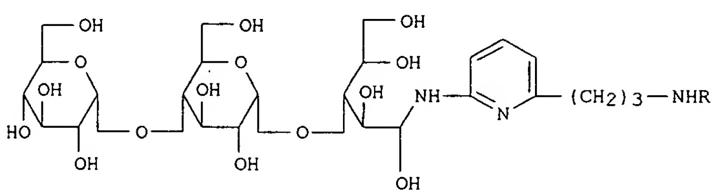


=> d bib abs 126 1

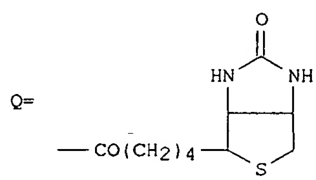
L26 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:95021 HCAPLUS
DN 124:146737
TI Method for fluorescent labeling of sugars and preparation of complex carbohydrates
IN Kusumoto, Shoichi; Fukase, Koichi
PA Seikagaku Kogyo Co Ltd, Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 07252288	A2	19951003	JP 1994-41545	19940311

GI



I



AB A fluorescent labeling method involves reductive amination of a sugar compd. having at least a reducing sugar terminus with a 2-**aminopyridine** deriv. having a N-protected aminoalkyl at the 6-position followed by deprotection of the NH2 group. The preferred protective is a urethane or haloacetyl group and is deprotected under basic or acidic condition or by redn., preferably using aq. piperidine for the deprotection under basic condition. A prepn. of a **complex** carbohydrate involves reductive amination of a sugar compd. having at least a reducing sugar terminus with a 2-**aminopyridine** deriv. having a N-protected aminoalkyl at the 6-position followed by N-deprotection to obtain the sugar-linked 2-amino-6-amino-**alkylpyridine** deriv., and reacting the amino group of the 6-aminoalkyl group of the latter compd. with an org. compd. having a functional group capable of linking to the amino group directly or via a spacer having a functional group (e.g CO2H) capable of linking to the amino group. Preferred org. group is a sugar, protein, peptide, amino acid, fat, **nucleic acid**, nucleotide, nucleoside, biotin, or synthetic **polymer**. Thus, 2-tritylamino-6-(3-trifluoroacetylaminopropyl)**pyridine**, obtained by redn. of 2-tritylamino-6-(2-cyanoethyl)**pyridine** with LiAlH4 to 2-tritylamino-6-(2-aminoethyl)**pyridine** followed by reaction with trifluoroacetic anhydride, was stirred in a 1:1 mixt. of AcOH-MeOH to give, after silica gel chromatog. and converting the partial AcOH salt to the **free amine** by extn. with aq. satd. NaHCO3, 2-amino-6-(6-trifluoroacetylaminopropyl)**pyridine**. The latter compd. (27.8 .mu.mol) and 5.55 .mu.mol maltotriose were heated in a sealed tube at 90.degree. for 3 h, cooled, and after adding a soln. of 6.55 mg

BH3.Me2NH in 33.5 mL AcOH, heated at 80.degree. for 1 h in the sealed tube to give, after HPLC purifn. using a Cosmosil 5C18AR column, maltotritol deriv. (I; R = COCF3), which was treated with 1 M aq. piperidine to give 100% I (R = H). The latter compd. was condensed with biotin N-hydroxysuccinimide ester in 0.5% NaHCO3-DMF to give, after the similar HPLC purifn., 65% the biotin-labeled maltotritol deriv. I (R = Q).

=> d bib abs l31 1

L31 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:468928 HCAPLUS
DN 127:203018
TI Conjugated polyamines and reproductive development: biochemical, molecular and physiological approaches
AU Martin-Tanguy, Josette
CS Groupe de Biologie Vegetale, UMR-CNRS 1853, Univ. de Rennes I, Rennes, F-35042, Fr.
SO Physiol. Plant. (1997), 100(3), 675-688
CODEN: PHPLAI; ISSN: 0031-9317
PB Munksgaard
DT Journal
LA English
AB Whole tobacco plants contg. the root-inducing, left-hand transferred **DNA** (Ri TL-**DNA**) display a transformed phenotype, that includes alterations in a no. of developmental processes, such as floral induction, flowering and reprodn. The authors show that the entire Ri TL-**DNA** is responsible for repression of ornithine and tyrosine decarboxylases while it exerts no effect on transferase and the Me transferase activities. Evidence is provided that two genes from the Ri TL-**DNA**, rolA and rolC, alter **polyamine** metab. as well as floral induction and flowering. Thus, plants transformed by the rolC gene (under the control of the 35S promoter from cauliflower mosaic virus) were male-sterile (non-viable pollen) and female fertility was reduced by approximatively 80%. A constitutive overexpression of the rolC gene may directly or indirectly cause inhibition of the accumulation of water-insol. amine **conjugates** located in the anthers and all the Me transferases, leading to increases of ornithine decarboxylase, phenylalanine ammonia lyase and putrescine caffeoyl-CoA transferase. The results suggest that male sterility is assocd. with catabolic processes exerted at the level of water-insol. amine **conjugates** and support the view that diamine oxidase may be involved in the regulation of the amine concn. during sexual differentiation, a factor that should be considered when attempting to decipher the mechanisms of control of sexual differentiation. The rolC gene could be useful in detg. the role of diamine oxidase in the physiol. of flowering. These results suggest that elevated free **polyamine** and water-sol. **polyamine** levels (located in the ovaries) contribute to abnormal floral development. The transformed phenotype due to P35S-rolA (the rolA gene fused to the 35S promoter) consisted of inhibited or delayed flowering, and altered floral morphol. in the form of flower abortion. The effects of P35S-rolA on flowering and fertility are closely correlated with limitations in the accumulation of the water-sol. and -insol. amine **conjugates** and increase in accumulation of **free amines**, indicating that **amine conjugates** (via transferases) have important functions in floral induction, floral evocation and reprodn. Spermidine availability as well as tyramine availability (in **conjugated** forms) could be limiting factor(s) in sexual development in tobacco.

=> d bib abs l31 2

L31 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:130886 HCAPLUS
DN 126:261194
TI A luminescent europium complex for the sensitive detection of proteins and nucleic acids immobilized on membrane supports
AU Lim, Mark J.; Patton, Wayne F.; Lopez, Mary F.; Spofford, Kimberely H.; Shojaee, Negin; Shepro, David
CS Microvascular Res. Lab., Boston Univ., Boston, MA, 02215, USA
SO Anal. Biochem. (1997), 245(2), 184-195
CODEN: ANBCA2; ISSN: 0003-2697
PB Academic
DT Journal
LA English
AB Certain metal **complexes** selectively interact with proteins immobilized on solid-phase membrane supports to form brightly colored products. Detecting the absorbance of colorimetric stains is limited by the molar extinction coeff. of the product, however, Development of light-emitting **complexes** should improve detection sensitivity, but fluorescent labels described to date modify **free amino**, carboxyl, or sulfhydryl groups often rendering proteins unsuitable for further anal. Bathophenanthroline disulfonate (BPSA) forms a luminescent europium (Eu) **complex** that reversibly binds to proteins and **nucleic acids**. Anal. of charge-fractionated carrier ampholytes and synthetic **polymers** of different L-amino acids indicates the protein binding is chiefly through protonated .alpha.- and .epsilon.-amino side chains. Proteins or **nucleic acids** immobilized to a nitrocellulose or polyvinyl difluoride membrane by electroblotting, dot-blotting, or vacuum slot-blotting are incubated with the lanthanide **complex** at acidic pH. Membranes are rinsed, illuminated with UV light and the phosphorescence of BPSA-Eu is measured at 590 to 615 nm using a CCD camera of spectrofluorimeter. The linear dynamic range of the stain is 476- and 48-fold for protein and **DNA**, resp. A strong chelating agent such as EDTA combined with a shift to basic pH (pH 8-10) elutes BPSA-Eu from the membrane. The reversible nature of the protein staining procedure allows for subsequent biochem. analyses, such as immunoblotting, lectin staining, and mass spectrometry.

=> d bib abs l31 3

L31 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:719880 HCAPLUS
DN 126:11526
TI The design of a reactive surface with stimuli sensitivity towards temperature and pH
AU Nagasaki, Yukio; Kobayashi, Jun-Ya; Tsujimoto, Hirofumi; Kato, Masao; Kataoka, Kazunori; Tsuruta, Teiji
CS Department Materials Science and Technology, Science University Tokyo, Noda, 278, Japan
SO Nanobiology (1996), 4(1), 63-70
CODEN: NNOBE7; ISSN: 0958-3165
PB Gordon & Breach
DT Journal
LA English
AB Using the stimuli-sensitive heterotelechelic oligomer, poly(silamine), which was synthesized by our original synthetic method, **polymer** brushes on a glass surface were prepd. Since poly(silamine) has a vinylsilyl group at one end and a sec-amino group at the other end, the introduction of a trimethoxysilyl group was carried out using a radical addn. reaction of 3-trimethoxysilylpropanethiol to the end double-bond of poly(silamine), retaining the sec-amino group at the other end intact. The obtained **polymer** could be used as a surface modifier for glass to form a **polymer** brush. Surface properties of the poly(silamine) surface thus obtained can be controlled not only by the environmental pH but also by the temp. For example, with increasing temp. at const. pH, the .zeta.-potential of the poly(silamine) surface decreased, indicating that the deprotonation of poly(silamine) on the surface was promoted by increasing temp. Sec-**Amino** groups at the **free** end of the poly(silamine) on the surface were utilized for **conjugation** with a compd. which reacts with sec-amine such as **DNA** and protein. The poly(silamine) surface is promising because not only can the surface characteristics be controlled by the surrounding environment but also by the **conjugation** with certain functional components at the free end of the **polymer** brushes.

=> d bib abs 131 4

L31 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:444291 HCAPLUS
DN 119:44291
TI A method for detection of hydroxyl radicals in the vicinity of biomolecules using radiation-induced fluorescence of coumarin
AU Makrigiorgos, G. M.; Baranowska-Kortylewicz, J.; Bump, E.; Sahu, S. K.; Berman, R. M.; Kassis, A. I.
CS Jt. Cent. Radiat. Ther., Harvard Med. Sch., Boston, MA, 02115, USA
SO Int. J. Radiat. Biol. (1993), 63(4), 445-58
CODEN: IJRBE7; ISSN: 0955-3002
DT Journal
LA English
AB A novel method is described to quantitate radiation-induced hydroxyl radicals in the vicinity of biomols. in aq. solns. Coumarin 3-carboxylic acid (CCA) is a nonfluorescent mol. that, upon interaction with radiation in aq. soln., produces fluorescent products. CCA was derivatized to its succinimidyl ester (SECCA) and coupled to **free** primary **amines** of albumin, avidin, histone-H1, **polylysine,** and an **oligonucleotide**. When SECCA-biomol. **conjugates** were irradiated, the relationship between induced fluorescence and dose was linear in the dose range examd. (0.01-10 Gy). The fluorescence excitation spectrum of irradiated SECCA-biomol. **conjugates** was very similar to that of 7-hydroxy-SECCA-biomol. **conjugates,** indicating the conversion of SECCA to 7-hydroxy-SECCA following irradn. Control studies in environments that excluded certain radiation-induced water radicals for both the **conjugated** and unconjugated forms of irradiated SECCA demonstrated the following: (1) the induction of fluorescence is mediated by the hydroxyl radical; (2) the presence of oxygen enhances induced fluorescence by a factor of .apprx.1.4; and (3) other primary water radicals and secondary radicals caused by interaction of primary water radicals with biomols. do not significantly influence the induced fluorescence. The data indicate that the induction of fluorescence on SECCA-biomol. **conjugates** records specifically the presence of the hydroxyl radical in the immediate vicinity of the irradiated biomol. The method is rapid and sensitive, uses std. instrumentation, and the sample remains available for further studies.

=> d bib abs l31 5

L31 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:566068 HCAPLUS
DN 117:166068
TI Interaction of acyclic and cyclic peralkylammonium compounds and DNA
AU Schneider, Hans Joerg; Blatter, Thomas
CS Fachrichtung Org. Chem., Univ. Saarlandes, Saarbruecken, W-6600/11, Germany
SO Angew. Chem. (1992), 104(9), 1244-6 (See also Angew. Chem., Int. Ed. Engl., 1992, 31(9), 1207-9)
CODEN: ANCEAD; ISSN: 0044-8249
DT Journal
LA German
AB Electrostatic binding of calf thymus B-DNA by amines was studied with regard to amine structure in the binding mechanism. **Free** energies of binding by various **amines** were compared. DNA binding response to amine protonation and alkyl chain length and flexibility were considered. Acyclic and macrocyclic polyammonium derivs. were used as models, and biol. polyamines were discussed.

=> d bib abs l31 6

L31 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:464026 HCAPLUS
DN 117:64026
TI RPC19, the gene for a subunit common to yeast RNA polymerases A (I) and C (III)
AU Dequard-Chablat, Michelle; Riva, Michel; Carles, Christophe; Sentenac, Andre
CS Dep. Biol. Cell. Mol., Cent. Etud. Nucl. Saclay, Gif-sur-Yvette, F91191, Fr.
SO J. Biol. Chem. (1991), 266(23), 15300-7
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Yeast RNA **polymerases** A (I) and C (III) share a subunit called AC19. The gene encoding AC19 has been isolated from yeast genomic **DNA** using **oligonucleotide** probes deduced from peptide sequences of the isolated subunit. This gene (RPC19) contains an intron-**free** open reading frame of 143 **amino** acid residues. RPC19 is a single copy gene that maps on chromosome II and is essential for cell viability. The amino acid sequence contains a sequence motif common to the Escherichia coli RNA **polymerase** .alpha. subunit, the Saccharomyces cervisiae AC40 and B44.5 subunits, the human hRPB33 product, and the CnjC **conjugation**-specific gene product of Tetrahymena. The 5'-upstream region contains a sequence element, the PAC box, that has been conserved in at least 10 genes encoding subunits of RNA **polymerases** A and C.

=> d bib abs l31 7

L31 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:651635 HCAPLUS
DN 115:251635
TI Using chelator-matrix conjugates to separate labeled compound from composition containing bound and unbound labeling reagents
IN Subramanian, Ramaswamy
PA AKZO N. V., Neth.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9106008	A1	19910502	WO 1990-US5772	19901010
	W: AU, CA, DK, FI, JP, KR				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	US 5244816	A	19930914	US 1989-419871	19891011
	ZA 9008095	A	19911127	ZA 1990-8095	19901009
	AU 9065471	A1	19910516	AU 1990-65471	19901010
	AU 656717	B2	19950216		
	EP 495878	A1	19920729	EP 1990-915696	19901010
	EP 495878	B1	19961127		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05503354	T2	19930603	JP 1990-514572	19901010
	AT 145560	E	19961215	AT 1990-915696	19901010
	ES 2097156	T3	19970401	ES 1990-915696	19901010
	FI 9201579	A	19920409	FI 1992-1579	19920409
	DK 9200488	A	19920410	DK 1992-488	19920410

PRAI US 1989-419871 19891011
WO 1990-US5772 19901010

AB A method for sepg. unbound labeling reagent from a compn. contg. bound and unbound labeling reagent comprises contacting the compn. with a chelator-matrix **conjugate** capable of binding the unbound labeling reagent. In the method, the labeling reagent is bound to peptide, protein, IgG, fragment of IgG, **nucleic acid**, or oligo- or **polynucleotide**; the labeling reagent is radioactive, fluorescent, luminescent, or paramagnetic; the chelator is a **polyaminopolycarboxylate** or a cyclopolyazacarboxylate; the matrix is a particulate (including its modified form), a membrane, or a vessel comprising an inside surface (e.g. syringe). In addn., a 2nd vessel comprising a chelator-IgG **conjugate** can be involved in the sepn.; a vessel comprising a plurality of chambers of which 1 chamber is **conjugated** with chelator and the 2nd is **conjugated** with chelator-IgG can also be used in the sepn. Thus, human serum albumin (HSA) was mixed with excess diethylenetriaminepentaacetic acid (DTPA) dianhydride; the mixt. was passed through a C-50 column; the HSA-DTPA soln. was then mixed with polystyrene beads. After washing with distd. water, DTPA-labeled HSA beads were obtained. The HSA-DTPA beads removed 111In from an acetate/citrate buffer. Washing with 1 M HCl removed all radioactivity, enabling the HSA-DTPA beads to be reused.

=> d bib abs l31 8

L31 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:650440 HCAPLUS
DN 115:250440
TI Aging mechanisms of proteins
AU Gillery, P.; Monboisse, J. C.; Maquart, F. X.; Borel, J. P.
CS Fac. Med., Univ. Reims, Reims, F 51095, Fr.
SO Diabete Metab. (1991), 17(1), 1-16
CODEN: DIMEDU; ISSN: 0338-1684
DT Journal; General Review
LA French
AB A review with 88 refs. All the living mols. appear to suffer from the deleterious effects of aging, but the primary mechanisms of this inexorable evolution are still unknown. In the case of proteins, two major types of chem. reactions participate in the aging phenomena: 1) structural transformations induced by the addn. of radicals by enzymic or nonenzymic reactions, 2) proteolytic cleavages. Among the reactions of the first group, the nonenzymic glycation is the more generalized, not only in diabetic patients but also in nondiabetic subjects. This glycation depends on the probabilities of encounters between circulating glucose mols. and **free amino** groups existing either at the N-terminal end of the polypeptide chains or on the lysyl side chains. These reactions are more frequent in the extracellular spaces and connective tissues because glucose circulates freely in these spaces, because the level of glucose is better controlled inside the cells (and even lower in diabetes mellitus), and finally because the proteins of these regions, such as the collagens, fibronectin and elastin, are relatively long lived, even if their life-span is really shorter than it was precedently believed. The binding of sugar residues to protein amino groups dets. frequent modifications of structure that often make the mol. inactive. For instance, when a glucose unit binds to a lysyl radical located in the active center of an enzyme, it suppresses the activity of this enzyme. More generally, in the case of the connective tissue proteins that participate in **complex** supramol. assemblies, the presence of addnl. radicals on some ponctual locations may interfere with the correct assocn. of mols. This is particularly true for basement membranes whose structure is impaired in diabetes. Glycation might also introduce abnormal crosslinks between polypeptides or modify the antigenic power of some proteins and explain the formation of autoantibodies. Another property of glycated proteins is their reaction with oxygen leading to the formation of superoxide. The binding of a reducing sugar on an amino function is followed by an Amadori rearrangement that forms a ketol group. Ketol groups have the property to transmit electrons to mol. oxygen, and to forming superoxide radicals. Superoxide is capable of degrading only one protein: collagen, but it is also able to transform itself into hydrogen peroxide and hydroxyl radicals, which are far more toxic than O2-. The result of the formation of these oxygen free radicals from glycated proteins is the initiation of the degrdn. of several types of proteins, like the collagens. Superoxide degrades type I collagen and liberates several small peptides which might be isolated and characterized. Then, nonspecific proteinases may intervene in order to complete the degrdn. into small peptides or amino acids. When oxygen free radicals penetrate through plasma membranes, particularly in the case of hydrogen peroxide, they may cause degrdns. of intracellular mols. For instance, H2O2 induces nicks in **DNA** mols. These nicks are repaired through a **complex** mechanism that comprises the formation of **polymers** of ADP-ribose bound the some enzyme proteins. This phenomenon of ADP-ribosylation merits to take place among the markers of protein aging.

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=> d bib abs l31 9
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L31 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:175207 HCAPLUS
DN 112:175207
TI Labelling of DNA with a non-radioactive analog of dGTP
AU Gillam, I. C.; Tener, G. M.
CS Dep. Biochem., Univ. British Columbia, Vancouver, BC, V6T 1W5, Can.
SO Nucleosides Nucleotides (1989), 8(8), 1453-62
CODEN: NUNUD5; ISSN: 0732-8311
DT Journal
LA English
AB 8-Bromo-2'-deoxyguanosine 5'-phosphate reacts with mercaptoethylamine. Oxidn. of the reaction mixt. generates a disulfide with a **free** aliph. **amino** group. Biotinylation yields an analog of dGMP, Bio-15-dGMP. The triphosphate, Bio-15-dGTP may be incorporated into **DNA** by **DNA polymerase** I of Escherichia coli and detected by reagents **conjugated** to avidin.

=> d bib abs l31 10

L31 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:626177 HCAPLUS
DN 109:226177
TI Synthesis and application of fluorescent labeled nucleotides to assay DNA damage
AU Kelman, David J.; Lilga, Kenneth T.; Sharma, Minoti
CS Dep. Biophys., Roswell Park Mem. Inst., Buffalo, NY, 14263, USA
SO Chem.-Biol. Interact. (1988), 66(1-2), 85-100
CODEN: CBINA8; ISSN: 0009-2797
DT Journal
LA English
AB A facile method was developed to covalently attach a fluorophore to the 5'-phosphate of a **nucleic acid**. The procedure, illustrated by coupling 5'-dNmp (N = A,C,G,T) with dansyl chloride involves 5'-phosphoramidation with ethylenediamine (EDA) followed by **conjugation** of the **free** aliph. **amino** group of the phosphoramidate with dansyl chloride. This method is also applicable to multi-incorporation of fluorescent labels in the **nucleic acids**. The reaction of 5'-Amp with a **polyamine** such as poly(L-lysine) (PLL, mol. wt., 4000) resulted in a phosphoramidate with multiple amino groups which after isolation and **conjugation** with fluorescamine gave dAmp with multilabeled fluorophores. A condition was devised to sep. the 4 dansylated mononucleotides of **DNA**, **conjugated** via ethylenediamine linker, by reversed-phase HPLC. The elution profile could be monitored with a variable wavelength detector at 254 nm and 340 nm corresponding to the absorption of the nucleotides and the dansyl moiety, resp. The detection limit was 2 nmol at 254 nm. The use of a fluorescence detector enhanced the detection sensitivity to a sub-picomole level (200 fmol). Samples of a **DNA** model, d(pCpGpTpA) and calf-thymus **DNA** were digested enzymically to 5'-mononucleotides and labeled with dansyl chloride. HPLC anal. of the dansylated digests from these samples, both before and after irradn., suggest that the combination of enzymic digestion and fluorescence postlabeling could be a novel approach to assay **DNA** damage.

=> d bib abs l31 11

L31 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:151984 HCAPLUS
DN 106:151984
TI Biochemistry of terminal deoxynucleotidyltransferase (TdT): characterization and mechanism of inhibition of TdT by P1,P5-bis(5'-adenosyl) pentaphosphate
AU Pandey, Virendranath; Modak, Mukund J.
CS New Jersey Med. Sch., Univ. Med. Dent. New Jersey, Newark, NJ, 07103, USA
SO Biochemistry (1987), 26(7), 2033-8
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The catalysis of **DNA** synthesis of calf thymus TdT was strongly inhibited in the presence of Ap5A, whereas replicative **DNA** **polymerases** from mammalian, bacterial, and oncornaviral sources were totally insensitive to Ap5A addn. The Ap5A-mediated inhibition of TdT appeared to occur via its interaction at both the substrate-binding and primer-binding domains as judged by (a) classical competitive inhibition plots with respect to both substrate deoxynucleoside triphosphate (dNTP) and **DNA** primer and (b) inhibition of UV light-mediated crosslinking of substrate dNTP and oligomeric **DNA** primer to their resp. binding sites. Further kinetic analyses of Ap5A inhibition revealed that the dissocn. const. of the Ap5A-enzyme **complex**, with either substrate binding or primer binding domain participating in the **complex** formation, was .apprx.6-fold higher (Ki = 1.5 .mu.M) compared to the dissocn. const. (Ki = 0.25 .mu.M) of the Ap5A-TdT **complex** when both domains were available for binding. In order to study the binding stoichiometry of Ap5A to TdT, an oxidized deriv. of Ap5A, which exhibited identical inhibitory properties as its parent compd., was employed. The oxidn. product of Ap5A, presumably a tetraaldehyde deriv., bound irreversibly to TdT when inhibitor-enzyme **complex** was subjected to borohydride redn. The presence of aldehyde groups in the oxidized Ap5A appeared essential for inhibitory activity since its redn. to alc. via borohydride redn. or its linkage to **free amino** acids prior to use an an inhibitor rendered it completely ineffective. With use of a tritiated oxidn. product of Ap5A, a binding stoichiometry of 1 mol of Ap5A to 1 mol of TdT was obsd. Thus, a single Ap5A mol. appears to span across both the substrate and primer binding site domains in TdT.

=> d bib abs l31 12

L31 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:136962 HCAPLUS
DN 96:136962
TI Contacts between Escherichia coli RNA polymerase subunits and lac UV5 promoter nucleotides
AU Chenchik, A. A.; Bibilashvili, R. Sh.; Mirzabekov, A. D.; Shik, V. V.
CS Inst. Mol. Biol., Moscow, USSR
SO Mol. Biol. (Moscow) (1982), 16(1), 34-46
CODEN: MOBIBO; ISSN: 0026-8984
DT Journal
LA Russian
AB A cloned restriction endonuclease EcoRI fragment of **DNA** contg. the lacUV5 promoter of E. coli was partially depurinated by methylation with Me2SO4 and heating. Incubation of E. coli RNA **polymerase** (holoenzyme or subunits) with the treated **DNA** gave covalent **DNA** enzyme **complexes** when depurinated ribose residues in the **DNA** lay close enough to **free amino** groups of the enzyme to permit aldimine formation. .beta.-Elimination on aldimine formation cleaved the **DNA** to give a fragment which could be sequenced to det. the point of cleavage and, hence, the site of **DNA**-enzyme contact. The portion of the enzyme making contact could be detd. by redn. of the aldimine with NaBH4 and sepg. the covalent **complex** from other enzyme subunits and the rest of the **DNA**. The holoenzyme contacts the promoter between residues +34 and -47; groups of contact points with this region were discernible. The frequency of **DNA**-enzyme contact was approx. the same for both **DNA** strands. **DNA**-enzyme contacts were not restricted to regions of internal homol. In the absence of the .sigma. subunit, there was no **DNA**-enzyme contact in the Pribnow sequence, and only the .beta.1 subunit made contact in the vicinity of residue -35. The .alpha. subunit made no contact with the **DNA** in the presence or absence of .sigma..

=> d bib abs l31 13

L31 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:69288 HCAPLUS
DN 84:69288
TI Effects of poly(9-vinyladenine) and poly(1-vinyluracil) on messenger ribonucleic acid template activity
AU Reynolds, Fred H., Jr.; Pitha, Paula M.; Chuang, Ronald; Cheng, Tu-Chen; Kazazian, Haig H., Jr.; Grunberger, Dezider
CS Sch. Med., Johns Hopkins Univ., Baltimore, Md., USA
SO Mol. Pharmacol. (1975), 11(6), 708-15
CODEN: MOPMA3
DT Journal
LA English
AB The neutral **polynucleotide** analogues, poly(9-vinyladenine) [26747-12-6] and poly(1-vinyluracil) [25750-74-7], inhibited [3H]dTTP incorporation in a system contg. rabbit hemoglobin mRNA as template, oligo(dT) as primer, and purified avian myeloblastosis RNA-dependent **DNA polymerase** [9068-38-6]. The incorporation was inhibited 50% at an analogue concn. of 0.1 mM in base residues. **Complexes** of homopolynucleotides with vinyl **polymers** were tested as templates in a cell-**free amino** acid-incorporating system prepd. from Krebs II ascites cells. Poly(9-vinyladenine) inhibited poly(U)-stimulated [14C]phenylalanine incorporation, while poly(1-vinyluracil) inhibited poly(A) [24937-83-5]-stimulated [14C]lysine incorporation. In neither case was the noncomplementary vinyl **polymer** inhibitory. Although poly(9-vinyladenine) had no effect on rabbit globin mRNA-stimulated **amino** acid incorporation in a cell-**free** system prepd. from the Krebs II ascites tumor, poly(1-vinyluracil) was slightly inhibitory, with 50% inhibition occurring at a concn. of 10 mM uracil residues. However, similar inhibition occurred with a prepn. of mRNA which did not contain the 3'-terminal poly(A) sequence, indicating that the inhibition occurring with high concns. of poly(1-vinyluracil) does not involve the 3'-terminal poly(A) of the mRNA. The radioactive proteins produced in the cell-free system both with and without vinyl **polymer** coelectrophoresed with rabbit globin marker. These results suggest that the 3'-terminal poly(A) sequence of mRNA does not function in cell-free protein synthesis. Furthermore, the failure of the vinyl **polymers** to significantly inhibit cell-free protein synthesis suggests that the mechanism of vinyl **polymer** inhibition of murine leukemia virus replication in mouse cells involves inhibition of RNA-dependent **DNA polymerase** rather than inhibition of viral protein synthesis.

=> d bib abs l45

L45 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1980:473280 HCAPLUS
DN 93:73280
TI Composite membrane with selective permeability
IN Kawaguchi, Takeyuki; Minematsu, Hiromasa; Takeya, Yutaka; Hayashi, Yuzuru; Hara, Shigeyoshi
PA Teijin Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 55049106	A2	19800409	JP 1978-122744	19781006

AB The title membranes are prepd. by painting or impregnating a microporous **membrane** with a polycarboxylic acid (or its deriv.)-polyalkylenepolyamine **polymer** (I) in a solvent and optionally with an acid acceptor in a solvent indifferent to the **membrane**, crosslinking with .gtoreq.1 compd(s). contg. .gtoreq.2 active groups to bond **free amino** groups of I, heating, and dyeing.
Thus, unwoven 180 g/m2 Dacron cloth fixed on a glass plate was coated with **12**.5% each of polysulfone and Methyl Cellosolve in DMF in 0.2 .mu. thickness, and gelled in H2O at room temp. to obtain a 40-70 .mu. thick unsym. polysulfone layer of pore size 5-60 nm and H2O permeability (3-7) .times. 10-2 g/cm2.s.atm at 2 kg/cm2 gage pressure. Adipic acid and triethylenetetramine (3.7 g each) was refluxed at 150.degree. with stirring to obtain a **polymer** [25085-21-6] contg. CO(CH2)4CONH(CH2CH2NH)3 units and 8.9 mequiv/g **free amino** groups, which was cooled and dild. with 350 mL H2O. The cloth was soaked in this soln. for 5 min, air-dried, soaked in 1% isophthaloyl chloride [99-63-8] in n-hexane, and heated in air at 120.degree.. When used for reverse osmosis of 0.5% aq. NaCl at 25.degree. and 42.5 kg/cm2 gage, H2O permeability was 95.8 initially or 92.3 L/m2 after 100 h and NaCl rejection was 97.8 or 98.2%, resp.

=> d bib abs l56 1

L56 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:375284 HCAPLUS
DN 127:86090
TI Methods and compositions for poly-.beta.-1-4-N-acetylglucosamine-containing chemotherapeutics
IN Vournakis, John N.; Finkielsztein, Sergio; Pariser, Ernest R.; Helton, Mike
PA Marine Polymer Technologies, Inc., USA
SO U.S., 97 pp. Cont.-in-part of U.S. Ser. No. 347,911.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 9

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5635493	A	19970603	US 1995-471545	19950606
	US 5622834	A	19970422	US 1993-160569	19931201
	US 5623064	A	19970422	US 1994-347911	19941201
	WO 9639122	A1	19961212	WO 1996-US5257	19960604

W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	AU 9659178	A1	19961224	AU 1996-59178	19960604

PRAI US 1993-160569 19931201
US 1994-347911 19941201
US 1995-470077 19950606
US 1995-470083 19950606
US 1995-470912 19950606
US 1995-471290 19950606
US 1995-471545 19950606
WO 1996-US5257 19960604

AB A purified, easily produced, high-mol.-wt., highly cryst. poly-.beta.(1.fwdarw.4)-N-acetylglucosamine (p-GlcNAc, chitin) polysaccharide species of reproducible compn. is prepd. from carefully controlled, aseptic cultures of marine microalgae, preferably diatoms. The p-GlcNAc is free of proteins and substantially **free** of single **amino** acids and other org. and inorg. contaminants. The p-GlcNAc and its derivs. such as polyglucosamine have therapeutic applications, e.g. in biodegradable drug delivery systems, cell encapsulation, and induction of hemostasis. They may be formulated into membranes, filaments, nonwoven textiles, sponges, gels, and 3-dimensional matrixes, and may find cosmetic and agricultural applications. Thus, covering an abrasion wound with a p-GlcNAc **membrane** promoted wound healing and reduced scar tissue formation. A p-GlcNAc **membrane** impregnated with 5'-FU and implanted on the surface of a colon tumor in vivo in mice retarded tumor growth.

=> d bib abs l56 2

L56 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:737674 HCAPLUS
DN 126:70612
TI Brain-derived peptides increase the expression of a blood-brain barrier GLUT1 glucose transporter reporter gene
AU Boado, Ruben J.
CS Department of Medicine and Brain Research Institute, UCLA School of Medicine, Los Angeles, CA, 90095, USA
SO Neurosci. Lett. (1996), 220(1), 53-56
CODEN: NELED5; ISSN: 0304-3940
PB Elsevier
DT Journal
LA English
AB The brain-derived peptide prepn. Cerebrolysin (Cl; EBEWE, Austria) increases the stability of blood-brain barrier (BBB)-GLUT1 transcript. To det. if the increase in BBB-GLUT1 mRNA stability is **assocd.** with an augmentation of gene expression, the present investigation studied the effect of Cl on the expression of a BBB-GLUT1-luciferase reporter gene in brain endothelial cultured (ECL) cells. Dose response studies showed that Cl markedly increased the expression of luciferase when the BBB-GLUT1-reporter gene was used. On the contrary, Cl produced no changes in the expression pattern of the control reporter gene, which lacks the GLUT1 regulatory sequence. Desensitization of the protein kinase C (PKC) receptor with the phorbol ester TPA, or inhibition with either 1-(5-**isoquinolinylsulfonyl**)-2-methylpiperazine (H7) or staurosporine, had no effect on the increased levels of luciferase induced by Cl. **Transfection** efficiency was detd. by measuring intracellular levels of the expression **vector** using a quant. **polymerase** chain reaction (PCR) assay. The data presented here demonstrate that Cl increases BBB-GLUT1 gene expression in ECL cells through a mechanism that appears to be independent of activation of PKC.

=> d bib abs 156 3

L56 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:503579 HCAPLUS
DN 121:103579
TI Method and apparatus for N-terminal peptide fragment collection
IN Nokihara, Kiyoshi
PA Shimadzu Corp., Kyoto, Japan
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 4344425	A1	19940630	DE 1993-4344425	19931224
	JP 06189784	A2	19940712	JP 1992-359495	19921224

PRAI JP 1992-359495 19921224
AB The method includes the following steps: acetylating the .epsilon.-amino groups of lysine in a protein in which the the N-terminal .alpha.-amino group is blocked; cleaving the .epsilon.-acetylated protein to obtain peptide fragments; reacting the peptide fragments with a functional group-contg. solid support which is suitable for forming a covalent bond with a **free amino** group of the cleaved peptide fragments; collecting the N-terminal-blocked peptide fragments (which were not immobilized in the preceding step) on a **polymer membrane** or a glass fiber filter which can react with a carboxyl group; and immobilizing the N-terminal-blocked peptide fragments on the **polymer membrane** or the glass fiber filter. According to the invention an N-terminal peptide fragment can be collected semiautomatically from a very small sample, and the amino acid sequence can be detd. without **complex** operations by the app. described. Since both the collection and the immobilization of the fragments can be done in the same container, dangers of contamination and loss are very slight.

=> d bib abs l56 4

L56 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:623431 HCAPLUS
DN 119:223431
TI Mutation of **histidine** 373 to leucine in cytochrome P450c17 causes 17.alpha.-hydroxylase deficiency
AU Monno, Satoshi; Ogawa, Hirofumi; Date, Takayasu; Fujioka, Motoji; Miller, Walter L.; Kobayashi, Masashi
CS Fac. Med., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan
SO J. Biol. Chem. (1993), 268(34), 25811-17
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The authors identified a new homozygous missense mutation His373 .fwdarw. Leu in the CYP17 gene of two sisters with 17.alpha.-hydroxylase deficiency with an elevated plasma aldosterone concn. by sequencing their genomic **DNAs** amplified by **polymerase** chain reaction. Using **polymerase** chain reaction-based site-directed mutagenesis, the authors prepd. a **DNA** that encoded the Leu373 mutant protein. COS-1 cells **transfected** with the mutant **DNA**, despite having an RNA hybridizable to the P450c17 cDNA, did not show 17.alpha.-hydroxylase and 17,20-lyase activities. Also, the cells were devoid of 11.beta.-hydroxylase and aldosterone synthase activities. To examine the mechanism by which the single amino acid change His373 .fwdarw. Leu eliminates activity, the authors expressed N-terminally modified P450c17 proteins with and without the Leu373 mutation in Escherichia coli and performed spectral studies. Membrane prepns. from E. coli cells expressing the wild-type form of the modified enzyme showed an absorption peak at 449 nm upon addn. of carbon monoxide in the reduced state and produced characteristic substrate-induced difference spectra, whereas those from the cells expressing the mutant form did not show these spectral changes. The 17.alpha.-hydroxylase and 17,20-lyase activities were obsd. only in E. coli cells expressing the wild-type enzyme. Thus, the His373 .fwdarw. Leu mutant does not incorporate the heme prosthetic group properly and suggest a crit. role of His373 in heme binding.

=> d bib abs l56 5

L56 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:77946 HCAPLUS
DN 118:77946
TI Antisense **oligonucleotides** to CFTR confer a cystic fibrosis phenotype on B lymphocytes
AU Krauss, Randy D.; Berta, Gabor; Rado, Thomas A.; Bubien, James K.
CS Gregory Fleming James Cystic Fibrosis Res. Cent., Univ. Alabama, Birmingham, AL, 35294, USA
SO Am. J. Physiol. (1992), 263(6, Pt. 1), C1147-C1151
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB Cystic fibrosis transmembrane conductance regulator (CFTR) is expressed at low levels in nonepithelial cells. CFTR is responsible for cell cycle-dependent cAMP-responsive Cl- permeability in lymphocytes. Agonist responsiveness of cystic fibrosis (CF) lymphocytes was restored by **transfection** with **plasmid** contg. wild type CFTR cDNA. CFTR mRNA was expressed in the B lymphoid cell line GM03299; however, quant. reverse transcriptase-**polymerase** chain reaction indicated that the level of CFTR mRNA was at least 1000-times lower than in T84 cells. CFTR protein could not be detected by Western blot or by immunopptn. of in vitro phosphorylated protein. Antisense **oligonucleotides** representing codons 1-12 of CFTR caused a complete inhibition of cell cycle-dependent Cl- permeability as detd. by 6-methoxy-N-(3-sulfopropyl)**quinolinium** fluorescence digital imaging microscopy, thereby inducing normal cells to acquire a CF phenotype. Thus, a CFTR-**assocd**. Cl- permeability is present and measurable in lymphocytes, even though CFTR mRNA and protein are expressed at low levels.

=> d bib abs 156 6

L56 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:54012 HCAPLUS
DN 116:54012
TI Influence of **histidine** on lipid peroxidation in sarcoplasmic reticulum
AU Erickson, Marilyn C.; Hultin, Herbert O.
CS Dep. Food Sci., Univ. Massachusetts, Amherst, Gloucester, MA, 01930, USA
SO Arch. Biochem. Biophys. (1992), 292(2), 427-32
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
AB The **free amino** acid, **histidine,** which exists at high concns. in some muscle systems, has previously been demonstrated to both inhibit and activate lipid peroxidn. in **membrane** model systems. This study sought to characterize the specificity of the **histidine** effect on iron-catalyzed enzymic and nonenzymic lipid peroxidn. Under conditions of activation (**histidine** added to the reaction mixt. after ADP and ferric ion), .alpha.-amino carboxylate, and pyrrole nitrogen were demonstrated by kinetic techniques to be involved in the activation of the enzymic system. It is hypothesized that a mixed ligand **complex** (iron, ADP, and **histidine**) formed may allow rapid redox cycling of iron. While increasing concns. of **histidine** increased stimulation in the enzymic system, the max. stimulation of a nonenzymic lipid peroxidn. system of ascorbate and ferric ion occurred at **histidine** concns. near 2.5 mM. Inhibition of a nonenzymic system (ferrous ion), on the other hand, occurred at all concns. of **histidine** when the ferrous ion was exposed to ADP prior to **histidine**. In enzymic systems, under conditions when the ferric ion was exposed to **histidine** prior to ADP, inhibition of lipid peroxidn. by **histidine** also occurred. The inhibitory effect of **histidine** was ascribed to the **imidazole** group and may arise from the formation of a different iron **complex** or the acceleration of **polymn.**, dehydration, and insolubilization of the ferric ion by the **imidazole** nitrogen. The demonstrated ability of **histidine** to affect in vitro lipid peroxidn. systems raises the possibility that this **free amino** acid may modulate lipid peroxidn. in vivo.

=> d bib abs 156 7

L56 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:478971 HCAPLUS
DN 113:78971
TI Concentration of aqueous solutions of amino acids
IN Aketo, Takaharu
PA Agency of Industrial Sciences and Technology, Japan
SO Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 02045454	A2	19900215	JP 1988-194340	19880805

AB Aq. soln. of an amino acid with pH greater than its isoelec. points was concd. via contacting with org. particles having an av. diam. of 0.1-5 .mu.m and contg. substances capable of **complexing** with the amino acid, thus encapsulating the amino acid inside the particles, sepg. these org. particles via passing the 2-phase mixt. through a **polymeric membrane** having pores < 20 times the av. diam. of the org. particles, dispersing them in H2O having a isoelec. point greater than that of the amino acid the **amino** acid, and recovering the **free** imino acid in an aq. soln. An aq. soln. (pH 10) of tryptophan was processed as above using Me(CH2)7NMe3Cl (I) as the **complexing** agent to give a soln. of tryptophan more concd. than one obtained without I.

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=> d bib abs 156 8

L56  ANSWER 8 OF 11  HCAPLUS  COPYRIGHT 2000 ACS
AN   1990:459837  HCAPLUS
DN   113:59837
TI   Concentration of aqueous solutions of amino acids
IN   Aketo, Takaharu
PA   Agency of Industrial Sciences and Technology, Japan
SO   Jpn. Kokai Tokkyo Koho, 4 pp.
     CODEN: JKXXAF
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   JP 02045453      A2    19900215      JP 1988-194339   19880805
     JP 04066858      B4    19921026
AB   Aq. soln. of an amino acid was concd. via contacting with org. particles
     having an av. diam. of 0.1-5 .mu.m and contg. substances capable of
     complexing with the amino acid, thus encapsulating the amino acid
     inside the particles, sepg. these org. particles via passing the 2-phase
     mixt. through a polymeric membrane having pores < 20
     times the av. diam. of the org. particles, dispersing them in H2O having
     isoelec. points less than that of the amino acid, and recovering
     the free amino acid in an aq. soln.  An aq. soln. (pH
     = 10) of phenylalanine was processed as above using Me(CH2)7NMe3Cl (I) as
     the complexing agent to give a soln. of tryptophan more concd.
     than one obtained without I.
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=> d bib abs 156 9

L56 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:245300 HCAPLUS
DN 112:245300
TI Hydrogen ion-selective electrodes based on neutral carriers: specific features in behavior and quantitative description of the electrode response
AU Egorov, V. V.; Lushchik, Ya. F.
CS Inst. Phys.-Chem. Probl., Beloruss. State Univ., Minsk, USSR
SO Talanta (1990), 37(5), 461-9
CODEN: TLNTA2; ISSN: 0039-9140
DT Journal
LA English
AB The influence was studied of the **membrane** and soln. compn. on the response of H+ ion-selective electrodes (ISE) with plasticized **polymer** and liq. membranes based on the neutral carriers N,N-dioctylaniline and tridecylamine in **assocn.** with trioctyloxybenzenesulfonic acid. The extn. processes at the **membrane**-soln. interface exert the main effect on the response limits by inducing essential changes in the activity of potential-detg. ions in the **membrane**. At low pH, the amine extn. of acids followed by neutralization (**free amines** binding in ion-pairs) is the relevant process, while at high pH it is th extn. of metal cations with amine salts of a lipophilic acid, with the consequent displacement of amine from the salts. Equations are suggested to represent the interphase potential of the H+-ISE membranes with allowance for these extn. processes. The exptl. electrode responses of both liq. and **polymer** membranes are shown to be well described by the equations for the interphase potential, thus indicating its dominant contribution to the **membrane** potential.

=> d bib abs 156 10

L56 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:469679 HCAPLUS
DN 109:69679
TI The preparation of poly (dT)-5'-transferrin **conjugates** and hybridization studies with poly (dA)-tailed linearized pBR322 **plasmid DNA**
AU Weiler, Solly; Ariatti, Mario; Hawtrey, Arthur O.
CS Dep. Biochem., Univ. Durban, Durban, 4000, S. Afr.
SO Biochem. Pharmacol. (1988), 37(12), 2405-10
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The formation of transferrin-**DNA complexes** intended for ligand-directed **transfection** studies has been achieved through a hybridization technique involving complementary homodeoxypolynucleotide chains attached to the participating protein and **DNA** species. Oligothymidylate residues (pT)n obtained by dicyclohexylcarbodiimide (CDI) **polymn**. of thymidine-5'-monophosphate (5'-TMP) were activated to the 5'-**imidazolides** which on incubation with transferrin yielded the 5'-linked phosphoramidates (pT)n-5'-transferrin. Homopolymeric chain extension of (pT)5-5'-transferrin by terminal transferase and dTTP at 30.degree. for 30 min yielded (pT)300-5'-transferrin. Cleavage of the phosphoramide link in the **polymer**-modified transferrin at 37.degree. was pronounced after 30 min although at 25.degree. hydrolysis was <5% after 4h. Poly(dT)-5'-transferrin readily hybridized with [3H]poly(dA)-tailed PstI-linearized pBR322 **DNA**. Resultant **complexes** were demonstrated by nitrocellulose filter binding and immunopptn. with anti-transferrin antibody. In contrast with poly(dT)-5'-transferrin, poly(dT)-5'-transferrin-poly(dA)-tailed pBR322 **DNA complexes** were stable at 37.degree., suggesting that annealing is followed by further stabilizing interactions between the **DNA** and protein components.

=> d bib abs 156 11

L56 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:529430 HCAPLUS
DN 91:129430
TI An infrared study of an anion exchange **membrane**
AU Heitner-Wirguin, Carla; Hall, Dorrit
CS Dep. Inorg. Anal. Chem., Hebrew Univ. Jerusalem, Jerusalem, Israel
SO J. Membr. Sci. (1979), 5(1), 1-14
CODEN: JMESDO; ISSN: 0376-7388
DT Journal
LA English
AB An anion exchange **membrane** with a backbone of polyethylene and a side chain of sulfonamide amine and the water sorbed on this **membrane** were studied by IR spectroscopy and thermogravimetric measurements. The various groups of this **membrane** as well as the changes that occur during chem. treatment are identified by these techniques. The changes induced by H bonding vary from **membrane** to **membrane**, and yield information on the conformations of the side chain and the factors that det. these conformations, such as steric hindrance, or the introduction of water or of ionic species. Some conformational information can be obtained from the anomalous relation between the sym. and antisym.-NH2 stretchings in the unsubstituted amines. Other structural features are the differences in the no. of configurations that occur between a **membrane** that contains a disubstituted **amine** in the **free** state and one in which **complex** ionic species are sorbed. Water in the **membrane** is sorbed, bound and affected by the structure of the **membrane**. The amt. of water in the **membrane** is small enough to be all water of hydration. The existence of 2 types of sorbed water is shown by the thermogravimetric measurements.

=> d bib abs l73 1

L73 ANSWER 1 OF 57 MEDLINE
AN 2000334976 MEDLINE
DN 20334976
TI Identification of domains of the HPV11 E1 protein required for DNA replication in vitro.
AU Amin A A; Titolo S; Pelletier A; Fink D; Cordingley M G; Archambault J
CS Department of Biological Sciences, Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec, H7S 2G5, Canada.
SO VIROLOGY, (2000 Jun 20) 272 (1) 137-50.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200009
EW 20000904
AB The HPV E1 and E2 proteins along with cellular factors, are required for replication of the viral genome. In this study we show that in vitro synthesized HPV11 E1 can support **DNA** replication in a cell-free system and is able to cooperate with E2 to recruit the host **polymerase** alpha primase to the HPV origin in vitro. Deletion analysis revealed that the N-terminal 166 amino acids of E1, which encompass a nuclear localization signal and a cyclin E-binding motif, are dispensable for E1-dependent **DNA** replication and for recruitment of pol alpha primase to the origin in vitro. A shorter E1 protein lacking the N-terminal 190 **amino** acids supported cell-**free** **DNA** replication at less than 25% the efficiency of wild-type E1 and was active in the pol alpha primase recruitment assay. An even shorter E1 protein lacking a functional **DNA**-binding domain due to a truncation of the N-terminal 352 amino acids was inactive in both assays despite the fact that it retains the ability to associate with E2 or pol alpha primase in the absence of ori **DNA**. We provide additional functional evidence that E1 interacts with pol alpha primase through the p70 subunit of the **complex** by showing that p70 can be recruited to the HPV origin by E1 and E2 in vitro, that the domain of E1 (amino acids 353-649) that binds to pol alpha primase in vitro is the same as that needed for interaction with p70 in the yeast two-hybrid system, and that exogenously added p70 competes with the interaction between E1 and pol alpha primase and inhibits E1-dependent cell-free **DNA** replication. On the basis of these results and the observation that pol alpha primase competes with the interaction between E1 and E2 in solution, we propose that these three proteins assemble at the origin in a stepwise process during which E1, following its interaction with E2, must bind to **DNA** prior to interacting with pol alpha primase. Copyright 2000 Academic Press.

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=> d bib abs l73 2

L73  ANSWER 2 OF 57  MEDLINE
AN   2000029750      MEDLINE
DN   20029750
TI   Characterisation of the binding interaction between poly(L-lysine) and DNA
     using the fluorescamine assay in the preparation of non-viral gene
     delivery vectors.
AU   Read M L; Etrych T; Ulbrich K; Seymour L W
CS   CRC Institute for Cancer Studies, University of Birmingham, Birmingham,
     UK.
SO   FEBS LETTERS, (1999 Nov 12) 461 (1-2) 96-100.
     Journal code: EUH. ISSN: 0014-5793.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer Journals
EM   200002
EW   20000204
AB   A major factor limiting the development of non-viral gene delivery systems
     is the poor characterisation of polyelectrolyte complexes formed
     between cationic polymers and DNA. The present study
     uses the fluorescamine reagent to improve characterisation of
     poly(L-lysine) (pLL)/DNA complexes post-modified with
     a multivalent hydrophilic polymer by determining the
     availability of free amino groups. The results show
     that the fluorescamine reagent can be used to monitor the self-assembly
     reaction between pLL and DNA and the degree of surface
     modification of the resultant complexes with a hydrophilic
     polymer. This experimental approach should enable the preparation
     of fully defined complexes whose properties can be better
     related to their biological activity.
```

=> d bib abs l73 3

L73 ANSWER 3 OF 57 MEDLINE
AN 1998356282 MEDLINE
DN 98356282
TI Dual amino acid-selective and site-directed stable-isotope labeling of the human c-Ha-Ras protein by cell-free synthesis.
AU Yabuki T; Kigawa T; Dohmae N; Takio K; Terada T; Ito Y; Laue E D; Cooper J A; Kainosho M; Yokoyama S
CS Cellular Signaling Laboratory, Institute of Physical and Chemical Research (RIKEN), Wako, Saitama, Japan.
SO JOURNAL OF BIOMOLECULAR NMR, (1998 Apr) 11 (3) 295-306.
Journal code: BJM. ISSN: 0925-2738.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
AB We developed two methods for stable-isotope labeling of proteins by cell-free synthesis. Firstly, we applied cell-**free** synthesis to the dual **amino** acid-selective 13C-15N labeling method, originally developed for in vivo systems by Kainosho and co-workers. For this purpose, we took one of the advantages of a cell-**free** protein synthesis system; the **amino** acid-selective stable-isotope labeling is free of the isotope scrambling problem. The targets of selective observation were Thr35 and Ser39 in the effector region (residues 32-40) of the Ras protein **complexed** with the Ras-binding domain of c-Raf-1 (Raf RBD) (the total molecular mass is about 30 kDa). Using a 15-mL Escherichia coli cell-free system, which was optimized to produce about 0.4 mg of Ras protein per 1-mL reaction, with 2 mg each of DL-[13C']proline and L-[15N]threonine, we obtained about 6 mg of Ras protein. As the Pro-Thr sequence is unique in the Ras protein, the Thr35 cross peak of the Ras.Raf RBD **complex** was unambiguously identified by the 2D 1H-15N HNCO experiment. The Ser-39 cross peak was similarly identified with the [13C']Asp/[15N]Ser-selectively labeled Ras protein. There were no isotope scrambling problems in this study. Secondly, we have established a method for producing a milligram quantity of site-specifically stable-isotope labeled protein by a cell-free system involving amber suppression. The E. coli amber suppressor tRNATyrCUA (25 mg) was prepared by in vitro transcription with T7 RNA **polymerase**. We aminoacylated the tRNATyrCUA transcript with purified E. coli tyrosyl-tRNA synthetase, using 2 mg of L-[15N]tyrosine. In the gene encoding the Ras protein, the codon for Tyr32 was changed to an amber codon (TAG). This template **DNA** and the [15N]Tyr-tRNATyrCUA were reacted for 30 min in 30 mL of E. coli cell-free system. The subsequent purification yielded 2.2 mg of [15N]Tyr32-Ras protein. In the 1H-15N HSQC spectrum of the labeled Ras protein, only one cross peak was observed, which was unambiguously assigned to Tyr32.

=> d bib abs l73 4

L73 ANSWER 4 OF 57 MEDLINE
AN 97223733 MEDLINE
DN 97223733
TI A luminescent europium complex for the sensitive detection of proteins and nucleic acids immobilized on **membrane** supports.
AU Lim M J; Patton W F; Lopez M F; Spofford K H; Shojaee N; Shepro D
CS Boston University, Biological Sciences Department, Massachusetts 02215, USA.
NC HL-43875 (NHLBI)
HL-48553 (NHLBI)
SO ANALYTICAL BIOCHEMISTRY, (1997 Feb 15) 245 (2) 184-95.
Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
EW 19970703
AB Certain metal **complexes** selectively interact with proteins immobilized on solid-phase **membrane** supports to form brightly colored products. Detecting the absorbance of colorimetric stains is limited by the molar extinction coefficient of the product, however. Development of light-emitting **complexes** should improve detection sensitivity, but fluorescent labels described to date modify **free amino**, carboxyl, or sulfhydryl groups often rendering proteins unsuitable for further analysis. Bathophenanthroline disulfonate (BPSA) forms a luminescent europium (Eu) **complex** that reversibly binds to proteins and **nucleic acids**. Analysis of charge-fractionated carrier ampholytes and synthetic **polymers** of different L-amino acids indicates that protein binding is chiefly through protonated alpha- and epsilon-amino side chains. Proteins or **nucleic acids** immobilized to a nitrocellulose or polyvinyl difluoride **membrane** by electroblotting, dot-blotting, or vacuum slot-blotting are incubated with the lanthanide **complex** at acidic pH. **Membranes** are rinsed, illuminated with UV light and the phosphorescence of BPSA-Eu is measured at 590 to 615 nm using a CCD camera or spectrofluorimeter. The linear dynamic range of the stain is 476- and 48-fold for protein and **DNA**, respectively. A strong chelating agent such as ethylenediaminetetraacetic acid combined with a shift to basic pH (PH 8-10) elutes BPSA-Eu from the **membrane**. The reversible nature of the protein staining procedure allows for subsequent biochemical analyses, such as immunoblotting, lectin staining, and mass spectrometry.

=> d bib abs l73 5

L73 ANSWER 5 OF 57 MEDLINE
AN 93224811 MEDLINE
DN 93224811
TI A method for detection of hydroxyl radicals in the vicinity of biomolecules using radiation-induced fluorescence of coumarin.
AU Makrigiorgos G M; Baranowska-Kortylewicz J; Bump E; Sahu S K; Berman R M; Kassis A I
CS Department of Radiation Oncology, Harvard Medical School, Boston, MA 02115..
NC CA 15523 (NCI)
SO INTERNATIONAL JOURNAL OF RADIATION BIOLOGY, (1993 Apr) 63 (4) 445-58. Journal code: IRB. ISSN: 0955-3002.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199307
AB A novel method is described to quantitate radiation-induced hydroxyl radicals in the vicinity of biomolecules in aqueous solutions. Coumarin-3-carboxylic acid (CCA) is a non-fluorescent molecule that, upon interaction with radiation in aqueous solution, produces fluorescent products. CCA was derivatized to its succinimidyl ester (SECCA) and coupled to **free** primary **amines** of albumin, avidin, histone-H1, **polylysine**, and an **oligonucleotide**. When SECCA-biomolecule **conjugates** were irradiated, the relationship between induced fluorescence and dose was linear in the dose range examined (0.01-10 Gy). The fluorescence excitation spectrum of irradiated SECCA-biomolecule **conjugates** was very similar to that of 7-hydroxy-SECCA-biomolecule **conjugates**, indicating the conversion of SECCA to 7-hydroxy-SECCA following irradiation. Control studies in environments that excluded certain radiation-induced water radicals for both the **conjugated** and unconjugated forms of irradiated SECCA demonstrated that: (1) the induction of fluorescence is mediated by the hydroxyl radical; (2) the presence of oxygen enhances induced fluorescence by a factor of about 1.4, and (3) other primary water radicals and secondary radicals caused by interaction of primary water radicals with biomolecules do not significantly influence the induced fluorescence. The data indicate that the induction of fluorescence on SECCA-biomolecule **conjugates** records specifically the presence of the hydroxyl radical in the immediate vicinity of the irradiated biomolecule. The method is rapid and sensitive, uses standard instrumentation, and the sample remains available for further studies.

=> d bib abs l73 6

L73 ANSWER 6 OF 57 MEDLINE
AN 91332053 MEDLINE
DN 91332053
TI RPC19, the gene for a subunit common to yeast RNA polymerases A (I) and C (III).
AU Dequard-Chablat M; Riva M; Carles C; Sentenac A
CS Departement de Biologie Cellulaire et Moleculaire-Service de Biochimie et de Genetique Moleculaire, Centre d'Etudes Nucleaires de Saclay, Gif-sur-Yvette, France..
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Aug 15) 266 (23) 15300-7. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-M64991; GENBANK-S47700; GENBANK-S47692; GENBANK-S47693; GENBANK-S47390; GENBANK-S47394; GENBANK-M63977; GENBANK-M63978; GENBANK-M63926; GENBANK-M63255
EM 199111
AB Yeast RNA **polymerases** A (I) and C (III) share a subunit called AC19. The gene encoding AC19 has been isolated from yeast genomic **DNA** using **oligonucleotide** probes deduced from peptide sequences of the isolated subunit. This gene (RPC19) contains an intron-**free** open reading frame of 143 **amino** acid residues. RPC19 is a single copy gene that maps on chromosome II and is essential for cell viability. The amino acid sequence contains a sequence motif common to the Escherichia coli RNA **polymerase** alpha subunit, the Saccharomyces cerevisiae AC40 and B44.5 subunits, the human hRPB33 product, and the CnjC **conjugation**-specific gene product of Tetrahymena. The 5'-upstream region contains a sequence element, the PAC box, that has been conserved in at least 10 genes encoding subunits of RNA **polymerases** A and C.

=> d bib abs l73 7

L73 ANSWER 7 OF 57 MEDLINE
AN 88253513 MEDLINE
DN 88253513
TI Synthesis and application of fluorescent labeled nucleotides to assay DNA damage.
AU Kelman D J; Lilga K T; Sharma M
CS Department of Biophysics, Roswell Park Memorial Institute, Buffalo, NY 14263..
SO CHEMICO-BIOLOGICAL INTERACTIONS, (1988) 66 (1-2) 85-100.
Journal code: CYV. ISSN: 0009-2797.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198810
AB A facile method was developed to covalently attach a fluorophore to the 5'-phosphate of a **nucleic acid**. The procedure, illustrated by coupling 5'-dNmp (N = A,C,G,T) with 5-dimethylaminonaphthalene 1-sulfonyl chloride, commonly known as Dansyl chloride, involves 5'-phosphoramidation with ethylenediamine (EDA) followed by **conjugation** of the **free** aliphatic **amino** group of the phosphoramidate with Dansyl chloride. This method is also applicable to multi-incorporation of fluorescent labels in the **nucleic acids**. The reaction of 5'-Amp with a **polyamine** such as poly L-lysine (PLL, mol. wt., 4000) resulted in a phosphoramidate with multiple amino groups, which after isolation and **conjugation** with fluorescamine gave dAmp with multilabeled fluorophores. A condition was devised to separate the four dansylated mononucleotides of **DNA, conjugated** via ethylenediamine linker, by reverse phase HPLC. The elution profile could be monitored with a variable wavelength detector at 254 nm and 340 nm corresponding to the absorption of the nucleotides and the dansyl moiety, respectively. The detection limit was 2 nmol at 254 nm. The use of a fluorescence detector enhanced the detection sensitivity to a sub-picomole level (200 fmol). Samples of a **DNA** model, d(pCpGpTpA) and calf-thymus **DNA** were digested enzymatically to 5'-mononucleotides and labeled with Dansyl chloride. HPLC analysis of the dansylated digests from these samples, both before and after irradiation, suggests that the combination of enzymatic digestion and fluorescence postlabeling could be a novel approach to assay **DNA** damage.

=> d bib abs l73 8

L73 ANSWER 8 OF 57 MEDLINE
AN 87242397 MEDLINE
DN 87242397
TI Biochemistry of terminal deoxynucleotidyltransferase (TdT): characterization and mechanism of inhibition of TdT by P1, P5-bis(5'-adenosyl) pentaphosphate.
AU Pandey V; Modak M J
SO BIOCHEMISTRY, (1987 Apr 7) 26 (7) 2033-8.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198710
AB The catalysis of **DNA** synthesis by calf thymus terminal deoxynucleotidyltransferase (TdT) is strongly inhibited in the presence of Ap5A, while replicative **DNA polymerases** from mammalian, bacterial, and oncornaviral sources are totally insensitive to Ap5A addition. The Ap5A-mediated inhibition of TdT seems to occur via its interaction at both the substrate binding and primer binding domains as judged by classical competitive inhibition plots with respect to both substrate deoxynucleoside triphosphate (dNTP) and **DNA** primer and inhibition of ultraviolet light mediated cross-linking of substrate dNTP and oligomeric **DNA** primer to their respective binding sites. Further kinetic analyses of Ap5A inhibition revealed that the dissociation constant of the Ap5A-enzyme **complex,** with either substrate binding or primer binding domain participating in the **complex** formation, is approximately 6 times higher (Ki = 1.5 microM) compared to the dissociation constant (Ki = 0.25 microM) of the Ap5A-TdT **complex** when both domains are available for binding. In order to study the binding stoichiometry of Ap5A to TdT, an oxidized derivative of Ap5A, which exhibited identical inhibitory properties as its parent compound, was employed. The oxidation product of Ap5A, presumably a tetraaldehyde derivative, binds irreversibly to TdT when the inhibitor-enzyme **complex** is subjected to borohydride reduction. The presence of aldehyde groups in the oxidized Ap5A appeared essential for inhibitory activity since its reduction to alcohol via borohydride reduction or its linkage to **free amino** acids prior to use as an inhibitor rendered it completely ineffective.(ABSTRACT TRUNCATED AT 250 WORDS)

=> d bib abs 173 9

L73 ANSWER 9 OF 57 USPATFULL
AN 2000:131592 USPATFULL
TI Detection of nucleic acids and nucleic acid units
IN Graham, Duncan, Edinburgh, United Kingdom
Linacre, Adrian Matthew Thornton, Glasgow, United Kingdom
Munro, Callum Hugh, Pittsburgh, PA, United States
Smith, William Ewan, Glasgow, United Kingdom
Watson, Nigel Dean, Ayrshire, United Kingdom
White, Peter Cyril, Drymen, United Kingdom
PA University of Strathclyde, Glasgow, United Kingdom (non-U.S. corporation)
PI US 6127120 20001003
WO 9705280 19970213
AI US 1998-983486 19980421 (8)
WO 1996-GB1830 19960725
19980421 PCT 371 date
19980421 PCT 102(e) date
PRAI GB 1995-17955 19950725
DT Utility
EXNAM Primary Examiner: Riley, Jezia
LREP Dann, Dorfman, Herrell and Skillman
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN 22 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 2282
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the detection of target **nucleic acids** or **nucleic acid** units in a sample, by obtaining a SER(R)S spectrum for a SER(R)S-active **complex** containing, or derived directly from, the target. The **complex** includes at least a SER(R)S-active label, and optionally a target binding species containing a **nucleic acid** or **nucleic acid** unit. In this detection method, the concentration of the target present in the SER(R)S-active **complex**, or of the **nucleic acid** or unit contained in the target binding species in the SER(R)S-active **complex**, is no higher than 10.sup.-10 moles per liter. Additionally or alternatively, one or more of the following features may be used with the method: i) the introduction of a **polyamine**; ii) modification of the target, and/or of the **nucleic acid** or **nucleic acid** unit contained in the target binding species, in a manner that promotes or facilitates its chemi-sorption onto a SER(R)S-active surface; iii) inclusion of a chemi-sorptive functional group in the SER(R)S-active label. The invention also provides SER(R)S-active **complexes** for use in such a method, a kit for use in carrying out the method or preparing the **complexes** and a method for sequencing a **nucleic acid** which comprises the use of the detection method to detect at least one target nucleotide or sequence of nucleotides within the acid.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 173 10

L73 ANSWER 10 OF 57 USPATFULL
AN 2000:128468 USPATFULL
TI Purified mammalian monocyte antigens and related reagents
IN McClanahan, Terrill K., Sunnyvale, CA, United States
Gorman, Daniel M., Newark, CA, United States
Bolin, Laurel M., San Jose, CA, United States
PA Schering Corporation, Kenilworth, NJ, United States (U.S. corporation)
PI US 6124436 20000926
AI US 1996-600430 19960213 (8)
DT Utility
EXNAM Primary Examiner: Hutzell, Paula K.; Assistant Examiner: Ungar, Susan
LREP Keleher, Gerald P.; Ching, Edwin P.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2202
AB Cell surface antigens from mammals, reagents related thereto, including purified proteins, specific antibodies, and nucleic acids encoding said antigens. Methods of using said reagents and diagnostic kits are also provided.

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=> d bib abs l73 11


L73  ANSWER 11 OF 57  USPATFULL
AN     2000:124773  USPATFULL
TI     Compositions that specifically bind to colorectal cancer cells and
       methods of using the same
IN     Waldman, Scott A., Ardmore, PA, United States
       Pearlman, Joshua M., Philadelphia, PA, United States
       Barber, Michael T., Paoli, PA, United States
       Schulz, Stephanie, West Chester, PA, United States
       Parkinson, Scott J., Philadelphia, PA, United States
PA     Thomas Jefferson University, Philadelphia, PA, United States (U.S.
       corporation)
PI     US 6120995  20000919
AI     US 1997-908643  19970807 (8)
DT     Utility
EXNAM  Primary Examiner: Eyler, Yvonne
LREP   Woodcock Washburn Kurtz Mackiewicz & Norris LLP
CLMN   Number of Claims: 11
ECL    Exemplary Claim: 7
DRWN   1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 4997
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     A unique transcription product, CRCA-1, and alternative translation
       products generated thereform, are disclosed. The transcript and its
       translation products are markers for colorectal cells. Screening and
       diagnostic reagents, kits and methods for metastasized colorectal cancer
       are disclosed as are reagents, kits and methods for identifying
       adenocarcinomas as colorectal in origin. Compounds, compositions and
       methods of treating patients with metastasized colorectal cancer and for
       imaging metastasized colorectal tumors in vivo are disclosed.
       Compositions and methods for delivering active compounds such as gene
       therapeutics and antisense compounds to colorectal cells are disclosed.
       Vaccines compositions and methods of for treating and preventing
       metastasized colorectal cancer are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 14

L73  ANSWER 14 OF 57  USPATFULL
AN      2000:31209  USPATFULL
TI      Methods for making HLA binding peptides and their uses
IN      Kubo, Ralph T., San Diego, CA, United States
        Grey, Howard M., La Jolla, CA, United States
        Sette, Alessandro, La Jolla, CA, United States
        Celis, Esteban, San Diego, CA, United States
PA      Epimmune Inc., San Diego, CA, United States (U.S. corporation)
PI      US 6037135  20000314
AI      US 1993-159339  19931129 (8)
RLI     Continuation-in-part of Ser. No. US 1993-103396, filed on 6 Aug 1993,
        now abandoned which is a continuation-in-part of Ser. No. US 1993-27746,
        filed on 5 Mar 1993, now abandoned which is a continuation-in-part of
        Ser. No. US 1992-926666, filed on 7 Aug 1992, now abandoned
DT      Utility
EXNAM   Primary Examiner: Cunningham, Thomas M.
LREP    Townsend and Townsend and Crew LLP
CLMN    Number of Claims: 68
ECL     Exemplary Claim: 1
DRWN    36 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 13053
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Methods for making peptides comprising an HLA-A24.1-, HLA-A1-, HLA-A11-,
        and HLA-A3.2-restricted T cell epitope consisting of about 8-11 amino
        acid residues, and methods of making a peptide that binds to an
        HLA-A24.1, HLA-A1, HLA-A11, and HLA-A3.2 molecule at a dissociation
        constant of less than 500 nM.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 16

L73 ANSWER 16 OF 57 USPATFULL
AN 2000:18052 USPATFULL
TI **Membrane** anchor/active compound conjugate, its preparation and its uses
IN Jung, Gunther, Tubingen, Germany, Federal Republic of
Wiesmuller, Karl-Heinz, Tubingen, Germany, Federal Republic of
Metzger, Jorg, Tubingen, Germany, Federal Republic of
Buhring, Hans-Jorg, Tubingen, Germany, Federal Republic of
Becker, Gerhard, Ofterdingen, Germany, Federal Republic of
Bessler, Wolfgang, Hagelloch, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 6024964 20000215
AI US 1995-466695 19950606 (8)
RLI Division of Ser. No. US 1995-387624, filed on 13 Feb 1995, now abandoned which is a continuation of Ser. No. US 1993-84091, filed on 30 Jun 1993, now abandoned which is a continuation-in-part of Ser. No. US 1990-588794, filed on 27 Aug 1990, now abandoned Ser. No. Ser. No. US 1989-340833, filed on 20 Apr 1989, now abandoned And Ser. No. US 1992-966603, filed on 26 Oct 1992, now abandoned which is a continuation of Ser. No. US 1990-610222, filed on 8 Nov 1990, now abandoned , said Ser. No. US 588794 which is a continuation of Ser. No. US 1989-427914, filed on 24 Oct 1989, now abandoned which is a continuation of Ser. No. US 1988-229770, filed on 1 Aug 1988, now abandoned which is a continuation of Ser. No. US 1986-876479, filed on 20 Jun 1986, now abandoned
PRAI DE 1985-3522512 19850624
DE 1985-3546150 19851227
DE 1988-3813821 19880422
DE 1989-3937412 19891110
DT Utility
EXNAM Primary Examiner: Smith, Lynette R. F.; Assistant Examiner: Nelson, Brett
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 2092
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB According to certain embodiments, the invention relates to a method of producing antibodies employing an immunoconjugate produced by conjugating at least one **membrane**-anchoring compound with at least one partial sequence of a viral, bacterial, or protoral protein. The immunoconjugate has the advantage that it can be stored for a very long time even without cooling. According to certain embodiments, the invention relates to an immunoconjugate for the specific induction of cytotoxic T-lymphocytes which comprises a conjugate from at least one **membrane** anchor compound and a protein, containing at least one killer T-cell epitope, of a virus, a bacterium, a parasite or a tumor antigen, or at least one partial sequence containing at least one killer T-cell epitope of a viral, bacterial or parasite protein or of a tumor antigen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs l73 17

L73  ANSWER 17 OF 57  USPATFULL
AN      2000:9723  USPATFULL
TI      Unique nucleotide and amino acid sequence and uses thereof
IN      Summers, Max D., Bryan, TX, United States
        Braunagel, Sharon C., Bryan, TX, United States
        Hong, Tao, Bryan, TX, United States
PA      The Texas A & M University System, College Station, TX, United States
        (U.S. corporation)
PI      US 6017734  20000125
AI      US 1997-792832  19970130 (8)
RLI     Continuation-in-part of Ser. No. US 1996-678435, filed on 3 Jul 1996,
        now abandoned
PRAI    US 1995-955          19950707 (60)
DT      Utility
EXNAM   Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman,
        Robert
LREP    Arnold, White & Durkee
CLMN    Number of Claims: 56
ECL     Exemplary Claim: 1
DRWN    47 Drawing Figure(s); 24 Drawing Page(s)
LN.CNT 7846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Provided are hydrophobic targeting sequences, which may serve to target
        heterologous proteins to a variety of cellular membranes. In
        particular, the structural components of the nuclear envelope, or those
        components which become nucleus-associated, may be targeted with the
        sequences provided. Also provided are methods of targeting heterologous
        proteins to particular membranes, and the use of these
        targeted proteins in therapeutic, diagnostic and insecticidal
        applications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 19

L73  ANSWER 19 OF 57  USPATFULL
AN     1999:128751  USPATFULL
TI     Oligonucleotide analogs with an amino acid or a modified amino alcohol
       residue
IN     Ramasamy, Kandasamy, Laguna Hills, CA, United States
       Seifert, Wilfried E., La Jolla, CA, United States
PA     ICN Pharmaceuticals, Inc., Costa Mesa, CA, United States (U.S.
       corporation)
PI     US 5969135  19991019
AI     US 1995-551947  19951102 (8)
DT     Utility
EXNAM  Primary Examiner: Shah, Mukund J.; Assistant Examiner: Ngo, Tamthom T.
LREP   Crockett & Fish; Fish, Robert D.
CLMN   Number of Claims: 9
ECL    Exemplary Claim: 1
DRWN   33 Drawing Figure(s); 33 Drawing Page(s)
LN.CNT 2996
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     The present invention provides various novel oligonucleotide analogs
       having one or more properties that make the subject compounds superior
       to conventional oligonucleotides for use in procedures employing
       oligonucleotides. The compounds of the invention are oligonucleotide
       analogs in which the furanose ring of a naturally occurring nucleic acid
       is replaced with an amino acid or a modified amino alcohol residue. Some
       embodiments of the novel compounds of the invention are particularly
       useful for the antisense control of gene expression. The compounds of
       the invention may also be used as nucleic acid hybridization probes or
       as primers. Another aspect of the invention is to provide monomeric
       precursors of the oligonucleotide analogs of the invention. These
       monomeric precursors may be used to synthesize the subject
       polynucleotide analogs. Another aspect of the invention is to provide
       formulations of the subject polynucleotide analogs that are designed for
       the treatment or prevention of disease conditions. Yet another aspect of
       the invention is to provide methods for treating or preventing diseases,
       particularly viral infections and cell growth disorders. The subject
       disease treatment methods comprise the step of administering an
       effective amount of the subject polynucleotide analogs for use as
       antisense inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs 173 20

L73 ANSWER 20 OF 57 USPATFULL
AN 1999:113652 USPATFULL
TI Self-assembling polynucleotide delivery system
IN Szoka, Jr., Francis C., San Francisco, CA, United States
Haensler, Jean, San Francisco, CA, United States
PA Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5955365 19990921
AI US 1995-480445 19950607 (8)
RLI Division of Ser. No. US 1992-913669, filed on 14 Jul 1992, now abandoned
which is a continuation-in-part of Ser. No. US 1992-864876, filed on 3
Apr 1992, now abandoned
DT Utility
EXNAM Primary Examiner: Marschel, Ardin H.
LREP Koenig, Nathan P.Crosby, Heafey, Roach & May
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 1806
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a self-assembling polynucleotide delivery system comprising components aiding in the delivery of the polynucleotide to the desired address which are associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and **membrane**-permeabilization components, and subcellular localization components. Specific compounds useful in this system are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs 173 21

L73  ANSWER 21 OF 57  USPATFULL
AN     1999:109966  USPATFULL
TI     Opsonin-enhanced cells, and methods of modulating an immune response to
       an antigen
IN     Segal, Andrew H., Boston, MA, United States
PA     Whitenead Institute for Biomedical Research, Cambridge, MA, United
       States (U.S. corporation)
PI     US 5951976  19990914
AI     US 1997-826259  19970327 (8)
DT     Utility
EXNAM  Primary Examiner: Hutzell, Paula K.; Assistant Examiner: Bansal, Geetha
       P.
LREP   Banner & Witcoff, Ltd.
CLMN   Number of Claims: 22
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 2180
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Disclosed are methods and compositions wherein opsonin-enhanced cells,
       that is, cells which have been 1) modified so as to express an opsonin
       from a recombinant nucleic acid, 2) modified so as to express higher
       levels of an endogenous opsonin, or 3) mixed with an exogenous opsonin,
       when administered to a subject, modulate the immune response in the
       recipient to a selected antigen or antigens contained in or attached to
       the cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 22

L73 ANSWER 22 OF 57 USPATFULL
AN 1999:15110 USPATFULL
TI Method and system for delivering therapeutic agents
IN Lemelson, Jerome H., 930 Tahoe Blvd, Incline Village, NV, United States 89451-9436
PI US 5865744 19990202
AI US 1996-714211 19960916 (8)
DT Utility
EXNAM Primary Examiner: Lateef, Marvin M.; Assistant Examiner: Shaw, Shawna J.
CLMN Number of Claims: 16
ECL Exemplary Claim: 16
DRWN 3 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1451
AB A system and method are disclosed for internally delivering a therapeutic agent to a patient under the automatic control of a computer. A diagnostic imaging modality, such as a CAT or MRI scanning system, generates one or more images of the patient's anatomy showing an anatomical region into which it is desired to deliver the cellular transplants. For each such image, location coordinates with respect to a patient support means are calculated by the computer for each individual pixel making up the image. Location coordinates are then defined for a select body region corresponding to pixels of the anatomical image(s) designated by a user of the system to receive the therapeutic agent. The computer then operates a manipulator arm in order to position an injection tool such as an injection needle or catheter mounted on the arm adjacent to the select body region. In the case of an injection needle, the needle is inserted into the region at the appropriate depth, and an injector is operated under computer control to force a predetermined amount of a medium containing the therapeutic agent out of a lumen within the injection needle and into the select body region.

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=> d bib abs 173 25

L73  ANSWER 25 OF 57  USPATFULL
AN      1998:135057  USPATFULL
TI      Derivatives of 6,8-difluoro-7-hydroxycoumarin
IN      Gee, Kyle R., Springfield, OR, United States
        Haugland, Richard P., Eugene, OR, United States
        Sun, Wei-Chuan, Eugene, OR, United States
PA      Molecular Probes, Inc., Eugene, OR, United States (U.S. corporation)
PI      US 5830912  19981103
AI      US 1996-749684  19961115 (8)
DT      Utility
EXNAM   Primary Examiner: Trinh, Ba K.
LREP    Helfenstein, Allegra J.; Skaugset, Anton E.
CLMN    Number of Claims: 35
ECL     Exemplary Claim: 1,20,35
DRWN    11 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 2250
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      The present invention comprises 6,8-difluoro-7-hydroxycoumarins and
        derivatives of 6,8-difluoro-7-hydroxycoumarins, including reactive dyes,
        dye-conjugates and enzyme substrates. These fluorine-substituted
        fluorescent dyes typically possess greater photostability and lower pH
        sensitivity in the physiological pH range than their nonfluorinated
        analogs, exhibit less fluorescence quenching when conjugated to a
        substance, possess absorption and emission spectra that closely match
        those of their nonfluorinated analogs, and also exhibit higher quantum
        yields than their nonfluorinated analogs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 26

L73  ANSWER 26 OF 57  USPATFULL
AN      1998:79141  USPATFULL
TI      Polypeptide and anti-HIV agent prepared therefrom
IN      Matsumoto, Akiyoshi, Hino, Japan
        Waki, Michinori, Higashimurayama, Japan
PA      Seikagaku Corporation, Tokyo, Japan (non-U.S. corporation)
PI      US 5776899  19980707
        WO 9510534  19950420 ##STR1##
AI      US 1995-454235  19950613 (8)
        WO 1994-JP1706  19941012
                19950613  PCT 371 date
                19950613  PCT 102(e) date
PRAI    JP 1993-280346       19931014
DT      Utility
EXNAM   Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Harle, Jennifer
LREP    Pennie & Edmonds, LLP
CLMN    Number of Claims: 7
ECL     Exemplary Claim: 1
DRWN    2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1062
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       A polypeptide represented by formula (I), and one example of such
        polypeptide be represented as formula 1 is presented. The above
        presented polypeptide may be useful in a pharmaceutical composition as
        an antimicrobial or antiviral agent, specifically as an anti-HIV agent
        and as a component of the DNA-transfecting systems for gene
        therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d kwic 26

L73  ANSWER 26 OF 57  USPATFULL
AB        . . . a pharmaceutical composition as an antimicrobial or antiviral
        agent, specifically as an anti-HIV agent and as a component of the DNA-
      transfecting systems for gene therapy.
SUMM    . . . modified. The polypeptides of the present invention may be used
        as an anti-HIV reagent and as a component of the DNA-
      transfecting systems for gene therapy. As will be detailed in
        the Section 6, infra, the polypeptides of the invention have anti-HIV.
        . .
DETD    . . . selected from the group including but not limited to Bzl
        (benzyl), MBzl (4-methoxybenzyl), 4-MeBzl (4-methylbenzyl), Acm
        (acetamidomethyl), Trt (trityl), Npys (3-nitro-2-
      pyridinesulfenyl), t-Bu(t-butyl) or t-BuS (t-butylthio), and
        Mbzl, 4-MeBzl, Trt, Acm and Npys are preferred. A protecting group for
        the hydroxy group. . .
DETD    . . . DIPCDI (diisopropylcarbodiimide) method [Tartar, A. et al.,
        1979, J. Org. Chem. 44:5000], active-ester method, mixed or symmetrical
        acid anhydride method, carbonyldiimidazole method, DCC-HOBt
        (1-hydroxybenzotriazole) method [Konig W. et al., 1970, Chem. Ber.,
        103:788, 2024, 2034] or diphenylphosphoryl azide method, but preferably.
        . .
DETD    The DNA-transfection systems include the use of polycations,
        calcium phosphate, liposome fusion, retroviruses, microinjection,
        electroporation and protoplast fusion. However, all of these. . .
DETD    Recently, highly efficient DNA-transfection
        procedure using cationic lipid-DNA complex or cyclic
        amphipathic peptide-DNA complex [Legendre and Szoka,
        Jr., Proc. Natl. Acad. Sci. USA, 90, 893-897 (1993)] has been reported.
        The peptides that can form a transfecting complex
        with DNA include gramicidin S, tyrocidine, polymyxin B,
      polylysine and melittin all with cationic nature. Among these,
        the most effective cationic peptide is gramicidin S which is known as an
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amphipathic cyclic decapeptide antibiotic with .beta.-sheet conformation and can permeabilize and **disrupt** cell **membranes**.
Both a positive charge and amphipathic character of gramicidin S are thought to be important for the high **transfection**. Considering these structural characteristics, the polypeptides of this invention can be an alternative candidate of gramicidin S for **DNA complex** with high **transfecting** ability because of their strongly cationic and amphipathic nature with .beta.-sheet conformation.

DETD In fact, tachyplesin I, one of the parent molecule of the polypeptides of this invention, can permeabilize **membranes** and bind to DNA similarly to gramicidin S [Matsuzaki et al., Biochim. Biophys. Acta, 1070, 259-264 (1991) and Yonezawa et. . . .

DETD Therefore, the polypeptides of this invention may be used as a component of the DNA-**transfecting** systems for gene therapy.

DETD After the completion of the condensation reaction, coupling was carried out for the protection of the **free amino** groups using acetic anhydride (DMBHA resin).

DETD . . . in 1 ml of DMSO was added under ice-cooling. After 6 to 7 hours of stirring at room temperature, the **free amino** group was fluoresceinthiocarbamoylated.

=> d bib abs l73 27

L73 ANSWER 27 OF 57 USPATFULL
AN 1998:78944 USPATFULL
TI Diagnostic kits useful for selectively detecting microorganisms in samples
IN Sheiness, Diana K., Bothell, WA, United States
Adams, Trevor H., Buckinghamshire, England
Stamm, Michael R., Bothell, WA, United States
Cangelosi, Gerard A., Seattle, WA, United States
Britschgi, Theresa B., Seattle, WA, United States
Dix, Connie K., Arlington, WA, United States
PA Becton Dickinson Company, Franklin Lakes, NJ, United States (U.S. corporation)
PI US 5776694 19980707
AI US 1997-886999 19970702 (8)
RLI Continuation of Ser. No. US 1995-458319, filed on 2 Jun 1995, now abandoned which is a division of Ser. No. US 1993-133598, filed on 8 Oct 1993, now patented, Pat. No. US 5700636 which is a continuation-in-part of Ser. No. US 1992-896094, filed on 29 May 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-600334, filed on 19 Oct 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Horlick, Kenneth R.
LREP Highet, Esq., David W.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3118
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates, in general, to diagnostic kits for selectively detecting a prokaryotic microorganism and a eukaryotic microorganism in a sample wherein the cells of such microorganisms are lysed by combining the sample with a lysis solution and contacting the nucleic acid released from the microorganisms with selective nucleic acid probes through hybridization techniques. The present invention can be used for detecting microorganisms associated with vaginal disorders, e.g., Gardnerella vaginalis, Trichomonas vaginalis and Candida albicans. These kits may be used in a medical practitioner's private office or in a more structured clinical environment, such as a hospital, a commercial clinical microbiology laboratory or the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 173 28

L73 ANSWER 28 OF 57 USPATFULL
AN 1998:75716 USPATFULL
TI Peptide nucleic acids
IN Nielsen, Peter E., Hjortevanget 509, DK 2980 Kokkedal, Denmark
Buchardt, Ole, Sondergardsvej 73, DK 3500 Vaerlose, Denmark
Egholm, Michael, Johnstrup Alle 3, DK 1923 Frederiksberg, Denmark
Berg, Rolf H., Strandvaenget 6, DK 2960 Rungsted Kyst, Denmark
PI US 5773571 19980630
AI US 1996-595387 19960201 (8)
RLI Division of Ser. No. US 1993-54363, filed on 26 Apr 1993, now patented, Pat. No. US 5539082 which is a continuation-in-part of Ser. No. US 1993-108591, filed on 22 Nov 1993
DT Utility
EXNAM Primary Examiner: Marschel, Ardin H.
LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1415
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel class of compounds, known as peptide nucleic acids, bind complementary ssDNA and RNA strands more strongly than a corresponding DNA. The peptide nucleic acids generally comprise ligands such as naturally occurring DNA bases attached to a peptide backbone through a suitable linker.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs l73 29

L73  ANSWER 29 OF 57  USPATFULL
AN      1998:57716  USPATFULL
TI      Aptamers specific for biomolecules and methods of making
IN      Griffin, Linda, Atherton, CA, United States
        Albrecht, Glenn, Redwood City, CA, United States
        Latham, John, Palo Alto, CA, United States
        Leung, Lawrence, Hillsborough, CA, United States
        Vermaas, Eric, Oakland, CA, United States
        Toole, John J., Burlingame, CA, United States
PA      Gilead Sciences, Inc., Foster City, CA, United States (U.S. corporation)
PI      US 5756291  19980526
AI      US 1995-484192  19950607 (8)
RLI     Continuation of Ser. No. US 1992-934387, filed on 21 Aug 1992, now
        abandoned
DT      Utility
EXNAM   Primary Examiner: Zitomer, Stephanie W.
LREP    Bosse, Mark L.
CLMN    Number of Claims: 12
ECL     Exemplary Claim: 1
DRWN    6 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 8242
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A method for identifying oligomer sequences, optionally comprising
        modified base, which specifically bind target molecules such as serum
        proteins, kinins, eicosanoids and extracellular proteins is described.
        The method is used to generate aptamers that bind to serum Factor X,
        PDGF, FGF, ICAM, VCAM, E-selectin, thrombin, bradykinin, PGF2 and cell
        surface molecules. The technique involves complexation of the target
        molecule with a mixture of oligonucleotides containing random sequences
        and sequences which serve as primer for PCR under conditions wherein a
        complex is formed with the specifically binding sequences, but not with
        the other members of the oligonucleotide mixture. The complex is then
        separated from uncomplexed oligonucleotides and the complexed members of
        the oligonucleotide mixture are recovered from the separated complex
        using the polymerase chain reaction. The recovered oligonucleotides may
        be sequenced, and successive rounds of selection using complexation,
        separation, amplification and recovery can be employed. The
        oligonucleotides can be used for therapeutic and diagnostic purposes and
        for generating secondary aptamers.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 32

L73  ANSWER 32 OF 57  USPATFULL
AN     1998:17200  USPATFULL
TI     Dye labeled polymers as reagents for measuring polymer degradation
IN     Haugland, Richard P., Eugene, OR, United States
       Zhou, Mingjie, Eugene, OR, United States
PA     Molecular Probes, Inc., Eugene, OR, United States (U.S. corporation)
PI     US 5719031  19980217
AI     US 1996-696544  19960814 (8)
DT     Utility
EXNAM  Primary Examiner: Ceperley, Mary E.
LREP   Helfenstein, Allegra J.; Skaugset, Anton E.
CLMN   Number of Claims: 40
ECL    Exemplary Claim: 32
DRWN   7 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1307
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     This invention relates to polymers labeled with fluorescent dye to the
       point that significant fluorescence quenching occurs, such that
       degradation of the polymer results in fluorescence enhancement. The
       resulting fluorescence enhancement is useful for measuring the
       degradation of such polymers, for example as a result of enzymatic
       hydrolyis of a protein, carbohydrate, nucleic acid, or other natural or
       synthetic polymer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 35

L73  ANSWER 35 OF 57  USPATFULL
AN      97:115315  USPATFULL
TI      Sulfonated derivatives of 7-aminocoumarin
IN      Wang, Hui-Ying, Eugene, OR, United States
        Leung, Wai-Yee, Eugene, OR, United States
        Mao, Fei, Eugene, OR, United States
PA      Molecular Probes, Inc., Eugene, OR, United States (U.S. corporation)
PI      US 5696157  19971209
AI      US 1996-749753  19961115 (8)
DT      Utility
EXNAM   Primary Examiner: Trinh, Ba K.
LREP    Helfenstein, Allegra J.; Skaugset, Anton E.
CLMN    Number of Claims: 27
ECL     Exemplary Claim: 1,17,23
DRWN    2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1717
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      The present invention describes 7-aminocoumarin dyes that are
        substituted one or more times at the 3-, 6- and/or 8-positions by a
        sulfonic acid or a salt of a sulfonic acid, said dyes being useful as
        fluorescent probes or in the preparation of enzyme substrates, caged
        probes, or adducts with reducing sugars. The dyes of the invention
        optionally possess a reactive group useful for preparing fluorescent
        conjugates, which conjugates and methods for their preparation are
        described herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 37

L73  ANSWER 37 OF 57  USPATFULL
AN     97:73438  USPATFULL
TI     Heterodimeric receptor libraries using phagemids
IN     Barbas, Carlos, La Jolla, CA, United States
       Kang, Angray, Carlsbad, CA, United States
       Lerner, Richard A., La Jolla, CA, United States
PA     The Scripps Research Institute, La Jolla, CA, United States (U.S.
       corporation)
PI     US 5658727  19970819
       WO 9218619  19921029
AI     US 1994-133011  19940608 (8)
       WO 1992-US3091  19920410
              19940608  PCT 371 date
              19940608  PCT 102(e) date
DT     Utility
EXNAM  Primary Examiner: Ketter, James S.
LREP   Fitting, Thomas
CLMN   Number of Claims: 36
ECL    Exemplary Claim: 1
DRWN   19 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 5935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Filamentous phage comprising a matrix of cpVIII proteins encapsulating a
       genome encoding first and second polypeptides of an antogenously
       assembling receptor, such as an antibody, and a receptor comprised of
       the first and second polypeptides surface-integrated into the matrix via
       a filamentous phage coat protein membrane anchor domain fused to at
       least one of the polypeptides.
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 173 38

L73 ANSWER 38 OF 57 USPATFULL
AN 97:68583 USPATFULL
TI Nucleic acid probes useful for detecting microorganisms associated with vaginal infections
IN Sheiness, Diana K., Bothell, WA, United States
Cangelosi, Gerard A., Seattle, WA, United States
Britschgi, Theresa B., Seattle, WA, United States
PA Becton Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)
PI US 5654418 19970805
AI US 1995-460344 19950602 (8)
RLI Division of Ser. No. US 1993-133598, filed on 8 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-896094, filed on 29 May 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-600334, filed on 19 Oct 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Horlick, Kenneth R.
LREP Highet, Esq., David W.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3087
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to nucleic acid probes useful for the detection of microorganisms associated with vaginal disorders, for example Gardenerella vaginalis, Trichomonas vaginalis and Candida albicans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs l73 39

L73 ANSWER 39 OF 57 USPATFULL
AN 97:40632 USPATFULL
TI Trisubstituted .beta.-lactams and oligo .beta.-lactamamides
IN Ravikumar, Vasulinga, Carlsbad, CA, United States
PA Isis Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)
PI US 5629152 19970513
AI US 1994-283591 19940801 (8)
DT Utility
EXNAM Primary Examiner: Zitomer, Stephanie W.; Assistant Examiner: Rees, Dianne
LREP Woodcock Washburn Kurtz MacKiewicz & Norris
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2726
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel .beta.-lactam monomers bearing various functional groups are prepared. The novel .beta.-lactam monomers can be joined into oligomeric compounds via standard peptide linkages. Useful functional groups include nucleobases as well as polar groups, hydrophobic groups, ionic groups, aromatic groups and/or groups that participate in hydrogen bonding. The oligomeric compounds are useful as diagnostic and research reagents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 42

L73 ANSWER 42 OF 57 USPATFULL

SUMM . . . reports, Weber et al. (1983), Clinical Chemistry 29, pp. 1665-1672, Photoelectroanalytical Chemistry: Possible Interferences in Serum and Selective Detection of Tris(2,2'-**bipyridine**)ruthenium(II) in the Presence of Interferents, have discussed the problems associated with the use of this method to detect Ru-containing labels.. . . .

SUMM Extensive work has been reported on methods for detecting Ru(2,2'-**bipyridine**).sub.3.sup.2+ using photoluminescent, chemiluminescent, and electrochemiluminescent means: Rubinstein and Bard (1981), "Electrogenerated Chemiluminescence. 37. Aqueous Ecl Systems based on Ru(2,2'-**bipyridine**).sub.3.sup.2+ and Oxalate or Organic Acids", J. Am. Chem. Soc., 103, pp. 512-516; and White and Bard (1982), "Electrogenerated Chemiluminescence 41. . . .

SUMM . . . (II) Complexes in Monolayer Assemblies and at Water-Solid Interfaces", J. Am. Chem. Soc. 99, pp. 4947-4954, have described complexes of tris(2,2'-**bipyridine**)ruthenium(II) esterified with octadecanol or dehydrocholesterol, and have created monolayer films of these surfactant complexes. The complexes were photoluminescent. But when. . . .

SUMM . . . creating chemical moieties according to the present invention. The intermediates are the mono- and di-N-hydroxysuccinimide esters of ruthenium or osmium bis(2,2'-**bipyridine**) (2,2'-**bipyridine**-4,4'-dicarboxylic acid) and their salts. These compounds may be synthesized by means known in the art.

DETD . . . include plant pathogens such as fungi and nematodes. The term "subcellular particles" is meant to encompass, for example, subcellular organelles, **membrane** particles as from **disrupted** cells, fragments of cell walls, ribosomes, multienzyme complexes, and other particles which can be derived from living organisms. Nucleic acids. . . . this invention to include synthetic substances which chemically resemble biological materials, such as synthetic polypeptides, synthetic nucleic acids, and synthetic **membranes** , vesicles and liposomes. The foregoing is not intended to be a comprehensive list of the biological substances suitable for use. . . .

DETD . . . chemical moieties according to the present invention. The inventive intermediates are the mono- and di-N-hydroxysuccinimide esters of ruthenium or osmium bis(2,2'-**bipyridine**)(2,2'-**bipyridine**-4,4'-dicarboxylic acid) and their salts.

DETD The chemical structures of these intermediates are as follows. The mono-N-hydroxysuccinimide ester of ruthenium or osmium bis(2,2'-**bipyridine**) (2,2'-**bipyridine**-4,4'-dicarboxylic acid) includes ##STR1## wherein M is Ru or Os, n is the integer 1, 2, or 3, and salts and stereoisomers thereof. The di-N-hydroxysuccinimide esters of ruthenium- or osmiumbis-bis(2,2'-**bipyridine**) (2,2'-**bipyridine**-4,4'dicarboxylic acid) includes ##STR2## wherein M is Ru or Os, n is the integer 1, 2 or 3, and salts and. . . .

DETD . . . by means known to the art. A preferred method of synthesizing the ruthenium-containing compounds is to first react ruthenium dichlorobis (2,2'-**bipyridine**) with 2,2'-**bipyridine** -4,4'-dicarboxylic acid in a hot aqueous methanol solution of sodium bicarbonate. After acidification, an aqueous solution of NaPF.sub.6 is added to. . . .

DETD These intermediates are useful for labelling substances containing a **free amino** group capable of attacking the carboxylate ester, and thereby displacing N-hydroxysuccinimide. Use of these intermediates to label analytes of interest. . . .

DETD . . . the attaching linkage is an amide bond. The amide bond is formed between the substituent on the ligand and a **free amino** group on the substance that is to be labelled.

DETD . . . interest and the labelled analogue of the analyte can be any substances capable of participating in formation of a specific **complex** with a complementary material, such as for example, whole cells, subcellular particles, **nucleic acids**, polysaccharides, proteins, glycoproteins, lipoproteins, lipopolysaccharides, polypeptides, cellular metabolites, hormones,

pharmacological agents, tranquilizers, barbituates, alkaloids, steroids, vitamins, amino acids, sugars and non-biological **polymers**. Of particular interest are antibody-antigen-based methods. These methods are analogous to the well known radioimmunoassay, wherein an analyte of interest. . .

DETD Preparation of Ruthenium bis (2,2'-**bipyridine**) (2,2'-bi-**pyridine**-4,4'-dicarboxylic acid) bis(hexafluorophosphate)

DETD Sodium bicarbonate (0.40 g), ruthenium dichlorobis(2,2'-**bipyridine**)(0.40 g), and 2,2'-**bipyridine** -4,4'-dicarboxylic acid (0.30 g) were stirred in refluxing methanol (20 ml)-water (5 ml) for 9 hours. The resulting solution was cooled. . .

DETD Preparation of Active Ester of Ruthenium bis(2,2'-**bipyridine**) (2,2'-**bipyridine**-4,4'-dicarboxylic acid)

DETD . . . g) were dissolved in DMF (2 ml) with stirring, and cooled in an ice bath. A solution of ruthenium bis (2,2'-**bipyridine**) (2,2'-**bipyridine**-4,4'-dicarboxylic acid) (0.101 g, prepared as in Example I) dissolved in DMF (1 ml) was added, and the mixture was stirred. . .

=> d bib abs l73 42

L73 ANSWER 42 OF 57 USPATFULL
AN 95:86360 USPATFULL
TI Luminescent metal chelate labels and means for detection
IN Bard, Allen J., Austin, TX, United States
Whitesides, George M., Newton, MA, United States
PA Igen, Inc., Gaithersburg, MD, United States (U.S. corporation)
PI US 5453356 19950926
AI US 1993-159770 19931130 (8)
RLI Continuation of Ser. No. US 1990-604939, filed on 29 Oct 1990, now abandoned which is a division of Ser. No. US 1984-666987, filed on 31 Oct 1984, now abandoned
DT Utility
EXNAM Primary Examiner: Saunders, David
LREP Curtis, Morris & Safford; Evans, Barry
CLMN Number of Claims: 75
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1726
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A chemical moiety is disclosed which comprises a chemical, biochemical, or biological substance attached to one or more electrochemiluminescent organometallic compounds. In a preferred embodiment of the invention the substance is attached to one or more ruthenium-containing or osmium-containing luminescent organometallic compounds. Methods are disclosed for detecting very small amounts of the chemical moiety using chemiluminescent, electrochemiluminescent, and photoluminescent means. Compounds are disclosed which are useful for labelling substances of interest with ruthenium-containing and osmium-containing labels or other electrochemiluminescent labels. These labelled substances are useful in methods provided for detecting and quantifying analytes of interest in binding assays and competitive binding assays. The labelled substances are of particular use in homogeneous binding assays. These methods form the bases for systems designed to enable the rapid, efficient, and sensitive determination of a broad array of chemical, biochemical, and biological materials of interest.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 173 43

L73 ANSWER 43 OF 57 USPATFULL
AN 95:41013 USPATFULL
TI Non-nucleoside linkers for convenient attachment of labels to oligonucleotides using standard synthetic methods
IN Lin, Kuei-Ying, Fremont, CA, United States
Matteucci, Mark, Burlingame, CA, United States
PA Gilead Sciences, Foster City, CA, United States (U.S. corporation)
PI US 5414077 19950509
AI US 1994-237233 19940502 (8)
RLI Continuation of Ser. No. US 1990-594147, filed on 9 Oct 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-482943, filed on 20 Feb 1990, now abandoned
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Crane, L. Eric
LREP Morrison & Foerster
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1085
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pseudonucleosides and pseudonucleotides are useful in the synthesis of oligomers which contain these components as a means to derivatize the resulting oligonucleotide to useful substituents such as chelators, intercalators, or lipophilic compounds. In general, these pseudonucleotide components are of the formula: ##STR1## wherein each Y is independently O or S; each X is independently H, PO.sub.3.sup.-2, an activated nucleotide synthesis coupling moiety, a protecting group, a nucleoside, a nucleotide or a nucleotide sequence, or comprises a solid support;

F is a functional group capable of linking an additional moiety or said group already reacted to effect the binding of said additional moiety;

.quadrature. is an organic backbone which does not contain additional F or Y-X substituents and which is either achiral even when the Y-X substituents are different, or is a single enantiomer of a chiral compound;

with the proviso that at least one X is a nucleoside, nucleotide, nucleotide sequence, an activated nucleotide synthesis coupling moiety, or comprises a solid support, or F represents said functional group already reacted with an additional group. Oligonucleotides having the pseudonucleoside at the 3' terminus are particularly stable in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs l73 44

L73 ANSWER 44 OF 57 USPATFULL
AN 94:40006 USPATFULL
TI Luminescent metal chelate labels and means for detection
IN Bard, Allen J., Austin, TX, United States
Whitesides, George M., Newton, MA, United States
PA Igen, Inc., Rockville, MD, United States (U.S. corporation)
PI US 5310687 19940510
AI US 1991-789418 19911104 (7)
RLI Continuation of Ser. No. US 1986-858353, filed on 30 Apr 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-789113, filed on 24 Oct 1985, now patented, Pat. No. US 5235808 which is a continuation-in-part of Ser. No. US 1984-666987, filed on 31 Oct 1984, now abandoned
DT Utility
EXNAM Primary Examiner: Kim, Kay K.
LREP Curtis, Morris & Safford
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1996
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A chemical moiety is disclosed which comprises a chemical, biochemical, or biological substance attached to one or more electrochemiluminescent organometallic compounds. In a preferred embodiment of the invention the substance is attached to one or more ruthenium-containing or osmium-containing luminescent organometallic compounds. Methods are disclosed for detecting low concentrations of the chemical moiety using chemiluminescent, electrochemiluminescent, and photoluminescent means. Compounds are disclosed which are useful for labeling substances of interest with ruthenium-containing and osmium-containing labels or other electrochemiluminescent labels. These labeled substances are useful in methods provided for detecting and quantifying analytes of interest in binding assays and competitive binding assays. The labeled substances are of particular use in homogeneous binding assays. These methods form the bases for systems designed to enable the rapid, efficient, and sensitive determination of a broad array of chemical, biochemical, and biological materials of interest.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 173 45

L73 ANSWER 45 OF 57 USPATFULL
AN 93:104688 USPATFULL
TI Vectors and compounds for expression of human protein C
IN Bang, Nils U., Indianapolis, IN, United States
Beckmann, Robert J., Indianapolis, IN, United States
Jaskunas, S. R., Indianapolis, IN, United States
Lai, Mei-Huei T., Carmel, IN, United States
Little, Sheila P., Indianapolis, IN, United States
Long, George L., Indianapolis, IN, United States
Santerre, Robert F., Zionsville, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5270040 19931214
AI US 1992-907499 19920701 (7)
RLI Division of Ser. No. US 1988-215112, filed on 5 Jul 1988, now patented, Pat. No. US 5151268 which is a division of Ser. No. US 1985-699967, filed on 8 Feb 1985, now patented, Pat. No. US 4775624
DT Utility
EXNAM Primary Examiner: Patterson, Jr., Charles L.
LREP Norman, Douglas K.; Whitaker, Leroy
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 20 Drawing Figure(s); 20 Drawing Page(s)
LN.CNT 2792
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention comprises novel DNA compounds which encode human protein C activity. A variety of eukaryotic and prokaryotic recombinant DNA expression vectors have been constructed that comprise the novel protein C activity-encoding DNA and drive expression of protein C activity when transformed into an appropriate host cell. The novel expression vectors can be used to produce protein C derivatives, such as non-carboxylated, non-glycosylated, or non-hydroxylated protein C, and to produce protein C precursors, such as nascent or zymogen protein C, and to produce subfragments of protein C, such as active or inactive light and heavy chain. The recombinant-produced protein C activity is useful in the treatment and prevention of a variety of vascular disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs l73 50

L73  ANSWER 50 OF 57  USPATFULL
AN     92:82845  USPATFULL
TI     Conjugation of polymer to colony stimulating factor-1
IN     Shadle, Paula J., Belmont, CA, United States
       Koths, Kirston E., El Cerrito, CA, United States
       Moreland, Margaret, Berkeley, CA, United States
       Katre, Nandini, El Cerrito, CA, United States
       Laird, Walter J., Pinole, CA, United States
       Aldwin, Lois, San Mateo, CA, United States
       Nitecki, Danute E., Berkeley, CA, United States
       Young, John D., Walnut Creek, CA, United States
PA     Cetus Corporation, Emeryville, CA, United States (U.S. corporation)
PI     US 5153265  19921006
AI     US 1990-576415  19900830 (7)
       WO 1989-US270  19890123
              19900830  PCT 371 date
              19900830  PCT 102(e) date
RLI    Continuation-in-part of Ser. No. US 1988-146275, filed on 20 Jan 1988,
       now patented, Pat. No. US 4847325, issued on 11 Jul 1989
DT     Utility
EXNAM  Primary Examiner: Nutter, Nathan M.
LREP   McGarrigle, Philip L.; McLaughlin, Jane R.; Halluin, Albert P.
CLMN   Number of Claims: 33
ECL    Exemplary Claim: 1
DRWN   11 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 1918
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     A biologically active CSF-1 protein is selectively conjugated via
       certain amino acid residues or carbohydrate moieties to a water-soluble
       polymer selected from polyethylene glycol or polypropylene glycol
       homopolymers, polyoxyethylated polyols, or polyvinyl alcohol. The
       resulting conjugated CSF-1 is biologically active and has increased
       circulating half-life in mammals, compared to that of the unconjugated
       protein. The conjugated CSF-1 may be used to stimulate the immune
       response or to provide more cells to be stimulated.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d kwic 50

L73 ANSWER 50 OF 57 USPATFULL
DETD The recombinant CSF-1, produced in any host, whether eukaryotic or prokaryotic, may be **conjugated** to **polymers** via selected **amino** acid side groups, preferably **free amino** groups. Preferably, the **DNA** encoding CSF-1 is expressed in bacteria and the resulting CSF-1 is a homodimer after purification and refolding. If the **conjugation** is via a carbohydrate moiety, the host may be eukaryotic, or glycosylation may be carried out in vitro.

=> d bib abs l73 51

L73 ANSWER 51 OF 57 USPATFULL
AN 92:80669 USPATFULL
TI Methods of using recombinant human protein C
IN Bang, Nils U., Indianapolis, IN, United States
Beckmann, Robert J., Indianapolis, IN, United States
Jaskunas, S. Richard, Indianapolis, IN, United States
Lai, Mei-Huei T., Carmel, IN, United States
Little, Sheila P., Indianapolis, IN, United States
Long, George L., Indianapolis, IN, United States
Santerre, Robert F., Zionsville, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5151268 19920929
AI US 1988-215112 19880705 (7)
RLI Division of Ser. No. US 1985-699967, filed on 8 Feb 1985, now patented, Pat. No. US 4775624
DT Utility
EXNAM Primary Examiner: Stone, Jacqueline
LREP Norman, Douglas K.; Whitaker, Leroy
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 20 Drawing Figure(s); 20 Drawing Page(s)
LN.CNT 2825
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention comprises novel DNA compounds which encode human protein C activity. A variety of eukaryotic and prokaryotic recombinant DNA expression vectors have been constructed that comprise the novel protein C activity-encoding DNA and drive expression of protein C activity when transformed into an appropriate host cell. The novel expression vectors can be used to produce protein C derivatives, such as non-carboxylated, non-glycosylated, or non-hydroxylated protein C, and to produce protein C precursors, such as nascent or zymogen protein C, and to produce sub-fragments of protein C, such as active or inactive light and heavy chain. The recombinant-produced protein C activity is useful in the treatment and prevention of a variety of vascular disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs 173 52

L73  ANSWER 52 OF 57  USPATFULL
AN      92:20916  USPATFULL
TI      Generation and selection of novel DNA-binding proteins and polypeptides
IN      Ladner, Robert C., Ijamsville, MD, United States
        Guterman, Sonia K., Belmont, MA, United States
        Kent, Rachel B., Wilmington, MA, United States
        Ley, Arthur C., Newton, MA, United States
PA      Protein Engineering Corporation, Cambridge, MA, United States (U.S.
        corporation)
PI      US 5096815  19920317
AI      US 1989-293980  19890106 (7)
DT      Utility
EXNAM   Primary Examiner: Schwartz, Richard A.; Assistant Examiner: Ulm, John D.
LREP    Cooper, Iver P.
CLMN    Number of Claims: 42
ECL     Exemplary Claim: 1
DRWN    12 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 8344
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Novel DNA-binding proteins, especially repressors of gene expression,
        are obtained by variegation of genes encoding known binding protein and
        selection for proteins binding the desired target DNA sequence. A novel
        selection vector is used to reduce artifacts. Heterooligimeric proteins
        which bind to a target DNA sequence which need not be palindromic are
        obtained by a variety of methods, e.g., variegation to obtain proteins
        binding symmetrized forms of the half-targets and heterodimerization to
        obtain a protein binding the entire asymmetric target.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs l73 53

L73 ANSWER 53 OF 57 USPATFULL
AN 90:7546 USPATFULL
TI Microparticles comprising a biodegradable polymer controlling the release of an antimalaria active principle, pharmaceutical compositions comprising it and process for its preparation
IN Bontemps, Jose, Xhendremael, Belgium
Pirson, Philippe, Wezembeek-Oppem, Belgium
Falmagne, Jean-Bernard, Wavre, Belgium
Jerome, Robert, Tilff, Belgium
Teyssie, Philippe, Condroz, Belgium
Delattre, Luc, Oupeye, Belgium
Evrard, Brigitte, Verlaine, Belgium
PA Ire-Celltarg S.A., Fleurus, Belgium (non-U.S. corporation)
PI US 4897267 19900130
AI US 1988-225395 19880728 (7)
PRAI FR 1987-10802 19870730
DT Utility
EXNAM Primary Examiner: Page, Thurman K.
LREP Fleit, Jacobson, Cohn, Price, Holman & Stern
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 542
AB The present invention relates to microparticles containing an active principle against malaria, such as primaquine, one of its amino acid derivatives, or their **conjugates** with a hepatotropic **vector** or their pharmaceutically acceptable salts, and a biocompatible and biodegradable **polymer** controlling the kinetics of release of the active principle, like (DL)polylactide. The invention also relates to pharmaceutical compositions comprising microcapsules according to the invention. Lastly, the invention relates to processes for the preparation of microparticles as mentioned above, the processes comprising: dissolving the **polymer** in a volatile solvent, adding to this solution the active principle and possibly a substance regulating the size of the microparticles, and at the end of evaporation, recovering the microparticles by centrifugation and filtration.

=> d bib abs l73 54

L73 ANSWER 54 OF 57 USPATFULL
AN 89:56474 USPATFULL
TI Conjugation of polymer to colony stimulating factor-1
IN Shadle, Paula J., Richmond, CA, United States
Koths, Kirston E., El Cerrito, CA, United States
Moreland, Margaret, Berkeley, CA, United States
Katre, Nandini, El Cerrito, CA, United States
PA Cetus Corporation, Emeryville, CA, United States (U.S. corporation)
PI US 4847325 19890711
AI US 1988-146275 19880120 (7)
DT Utility
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Nutter, Nathan M.
LREP Halluin, Albert P.
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1560
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A biologically active CSF-1 protein is selectively conjugated via certain amino acid residues or carbohydrate moieties to a water-soluble polymer selected from polyethylene glycol or polypropylene glycol homopolymers, polyoxyethylated polyols, or polyvinyl alcohol. The resulting conjugated CSF-1 is biologically active and has increased circulating half-life in mammals, compared to that of the unconjugated protein. The conjugated CSF-1 may be used to stimulate the immune response or to provide more cells to be stimulated.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs l73 55

L73 ANSWER 55 OF 57 USPATFULL
AN 88:63998 USPATFULL
TI Vectors and compounds for expression of human protein C
IN Bang, Nils U., Indianapolis, IN, United States
Beckmann, Robert J., Indianapolis, IN, United States
Jaskunas, S. Richard, Indianapolis, IN, United States
Lai, Mei-Huei T., Carmel, IN, United States
Little, Shelia P., Indianapolis, IN, United States
Long, George L., Indianapolis, IN, United States
Santerre, Robert F., Zionsville, IN, United States
PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4775624 19881004
AI US 1985-699967 19850208 (6)
DT Utility
EXNAM Primary Examiner: Wiseman, Thomas G.; Assistant Examiner: Mays, Thomas D.
LREP Dahling, Gerald V.; Whitaker, Leroy
CLMN Number of Claims: 82
ECL Exemplary Claim: 12
DRWN 20 Drawing Figure(s); 20 Drawing Page(s)
LN.CNT 3091
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention comprises novel DNA compounds which encode human protein C activity. A variety of eukaryotic and prokaryotic recombinant DNA expression vectors have been constructed that comprise the novel protein C activity-encoding DNA and drive expression of protein C activity when transformed into an appropriate host cell. The novel expression vectors can be used to produce protein C derivatives, such as non-carboxylated, non-glycosylated, or non-hydroxylated protein C, and to produce protein C precursors, such as nascent or zymogen protein C, and to produce sub-fragments of protein C, such as active or inactive light and heavy chain. The recombinant-produced protein C activity is useful in the treatment and prevention of a variety of vascular disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d bib abs l73 56

L73  ANSWER 56 OF 57  USPATFULL
AN      87:74983  USPATFULL
TI      Silver stain for rapid, quantitative detection of polypeptides and
        nucleic acids
IN      Merril, Carl R., Rockville, MD, United States
PA      The United States of America as represented by the Department of Health
        and Human Services, Washington, DC, United States (U.S. government)
PI      US 4703016  19871027
AI      US 1986-859822  19860505 (6)
DT      Utility
EXNAM   Primary Examiner: Richman, Barry S.; Assistant Examiner: Hill, Jr.,
        Robert J.
LREP    Holman & Stern
CLMN    Number of Claims: 5
ECL     Exemplary Claim: 1,2
DRWN    3 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 869
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A simple, positive image forming silver stain which takes less than 15
        minutes to perform is disclosed for the detection of nanogram quantities
        of proteins and DNA on membranes and thin layer plates. This
        stain demonstrates a reproducible curvilinear relationship between
        silver density and the amount of protein or DNA, over an averaged
        concentration range from 1 nanogram to 300 nanograms for proteins and 10
        nanograms to 700 nanograms for DNA. The ease of staining proteins and
        DNA on membranes, combined with the stain's sensitivity and
        reproducibility, permits quantitative determination and assay of
        proteins and DNA.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs 173 57

L73  ANSWER 57 OF 57  USPATFULL
AN      84:39981  USPATFULL
TI      Drug delivery by polymeric carriers
IN      Tokes, Zoltan A., Los Angeles, CA, United States
        Rogers, Kathryn E., Pasadena, CA, United States
        Rembaum, Alan, Pasadena, CA, United States
PA      University of Southern California, Los Angeles, CA, United States (U.S.
        corporation)
PI      US 4460560  19840717
AI      US 1982-389537  19820618 (6)
DT      Utility
EXNAM   Primary Examiner: Nucker, Christine M.
LREP    Nilsson, Robbins, Dalgarn, Berliner, Carson & Wurst
CLMN    Number of Claims: 18
ECL     Exemplary Claim: 1,17,18
DRWN    3 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 783
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Anthracycline cancer drugs are covalently coupled to polymeric particles
        having a diameter of greater than about 0.5 microns to produce
        pharmaceutical preparations having enhanced cytostatic activity. The
        coupling of drugs to polymeric carriers shows increased activity against
        cancer cells, allows the bound drug to retain its cytostatic activity
        after repeated uses and shows an increase in activity against drug
        resistant cells.
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TEXT SEARCH II

NGUYEN 09/279,519

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=> d his

     (FILE 'HOME' ENTERED AT 10:20:15 ON 31 OCT 2000)

     FILE 'REGISTRY' ENTERED AT 10:20:39 ON 31 OCT 2000
L1            1 S 90-34-6
L2           46 S 90-34-6/CRN
L3          819 S 91-22-5/CRN
L4        70667 S PA/PCT
L5            0 S L2 AND L4
L6            2 S L3 AND L4
L7        32850 S PM/PCT
L8            0 S L2 AND L7
L9            2 S L3 AND L7
L10           1 S 26469-60-3
L11           1 S 26469-60-3/CRN

     FILE 'HCAPLUS' ENTERED AT 10:29:23 ON 31 OCT 2000
L12         693 S L1
L13         175 S L2
L14        1291 S L3
L15          25 S L10
L16           4 S L11
L17      660309 S DNA OR NUCLEIC OR OLIGONUCLEOTID? OR POLYNUCLEOTID? OR PLASMI
L18          57 S L17 AND L12-16
L19          25 S L17(L)L12-16
L20     1230012 S COMPLEX? OR ?CONJUGAT?
L21           8 S L19 AND L20
L22          22 S L18 AND L20
L23          22 S L21 OR L22
L24          32 S L12-16(L)?MEMBRAN?
L25          29 S L24 NOT L18
L26           0 S L25 AND PY>1997
L27           0 S L25 AND L17

     FILE 'USPATFULL' ENTERED AT 10:47:16 ON 31 OCT 2000
L28         135 S L1-3
L29           3 S L10-11
L30         138 S L28-29
L31      116823 S DNA OR NUCLEIC OR OLIGONUCLEOTID? OR POLYNUCLEOTID? OR PLASMI
L32          17 S L30 AND L31
L33      498913 S COMPLEX? OR ?CONJUGAT?
L34          12 S L32 AND L33
L35          11 S L34 AND ?MEMBRAN?
L36           7 S L35 AND ?POLYMER?
L37           2 S L35 AND (POLYAMID? OR POLYAMIN?)
L38           9 S L36 OR L37
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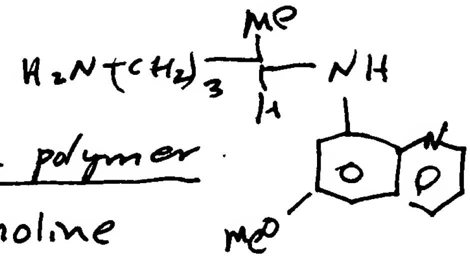
L1 =



L2 — searching for L1 in a polymer

L3 — searching for quinoline in a polymer

L10 → quinoline carboxylic acid

L11 → " " " in a polymer

L23 — 22 cites

L38 — 9 cites - not great

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=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2000 ACS
RN   90-34-6  REGISTRY
CN   1,4-Pentanediamine, N4-(6-methoxy-8-quinolinyl)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Quinoline, 8-[(4-amino-1-methylbutyl)amino]-6-methoxy- (6CI, 8CI)
OTHER NAMES:
CN   (.+-.)-Primaquine
CN   dl-Primaquine
CN   Neo-Quipenyl
CN   Primachin
CN   Primaquin
CN   Primaquine
CN   SN 13272
CN   WR 2975
FS   3D CONCORD
DR   57152-47-3
MF   C15 H21 N3 O
CI   COM
LC   STN Files:   AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, CIN,
       DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA,
       MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, SPECINFO, TOXLINE,
       TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
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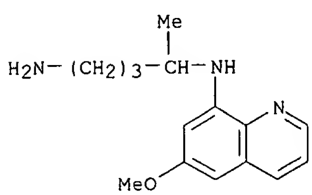


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     668 REFERENCES IN FILE CA (1967 TO DATE)
      53 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
     669 REFERENCES IN FILE CAPLUS (1967 TO DATE)
      37 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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=> d l10

L10  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2000 ACS
RN   26469-60-3  REGISTRY
CN   Quinolinecarboxylic acid (6CI, 7CI, 8CI, 9CI)  (CA INDEX NAME)
MF   C10 H7 N O2
CI   IDS, COM
LC   STN Files:   AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, IFICDB,
       IFIPAT, IFIUDB, TOXLIT, USPATFULL
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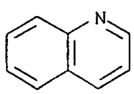

D1—CO_2H

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25 REFERENCES IN FILE CA (1967 TO DATE)
16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
25 REFERENCES IN FILE CAPLUS (1967 TO DATE)
 3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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=> d bib abs l23 1

L23 ANSWER 1 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:384398 HCAPLUS
DN 133:27336
TI Histidylated oligolysines increase the transmembrane passage and the biological activity of antisense **oligonucleotides**
IN Midoux, Patrick; Pichon, Chantal; Bello-Roufai, Mahajoub; Monsigny, Michel
PA I.D.M. Immuno-Designed Molecules, Fr.
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000032764	A1	20000608	WO 1999-EP8980	19991122

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI EP 1998-403015 19981202

AB The invention relates to a pos. charged oligomeric **conjugate,** contg. an oligomer with a d.p. from 5 to 50, preferably 10 to 40 and more preferably 20, formed from monomeric components having free NH3+ in a no. equal to or higher than 50% of the polymn. degree. In particular, the invention provides new oligomeric **conjugates** of histidylated oligolysine liable to allow the transfer of **oligonucleotides,** peptides and oligosides into cells. Histidylated oligolysines are designed which increase the uptake, the cytosolic delivery, and the nuclear accumulation of antisense **oligonucleotides** (ODN). Flow cytometry anal. showed a 10-fold enhancement of the ODN uptake in the presence of histidylated oligolysines. The intracellular localizations of fluorescein-labeled ODN and of rhodamine-labeled histidylated oligolysines were investigated by confocal microscopy. Histidylated oligolysines favor the cytosolic delivery of ODN from endosomes and increase their nuclear accumulation. In contrast, in their absence fluorescent ODN were not obsd. inside the nucleus but were distributed overwhelmingly within the vesicles in the cytosol. In addn., histidylated oligolysines yielded a more than 20-fold enhancement of the biol. activity of antisense ODN towards the inhibition of transient as well as constitutive gene expression.

RE.CNT 6
RE
(1) Goto, T; NUCLEOSIDES AND NUCLEOTIDES 1997
(2) Hatzenbuhler, N; US 5627270 A 1997 HCAPLUS
(3) Hisamitsu Pharmaceutical Co; EP 0727223 A 1996
(4) Idm Immuno Designed Molecules; WO 9822610 A 1998
(5) Midoux, P; BIOCONJUGATE CHEMISTRY 1998, V9(2), P260 HCAPLUS
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=> d bib abs 123 2

L23  ANSWER 2 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   2000:351162  HCAPLUS
DN   133:790
TI   New use of glutamate antagonists for the treatment of cancer
IN   Ikonomidou, Hrissanthi
PA   Germany
SO   Eur. Pat. Appl., 21 pp.
     CODEN: EPXXDW
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   EP 1002535        A1   20000524      EP 1998-250380   19981028
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
AB   New therapies can be devised based upon a demonstration of the role of
     glutamate in the pathogenesis of cancer.  Inhibitors of the interaction of
     glutamate with the AMPA, kainate, or NMDA receptor complexes are
     likely to be useful in treating cancer and can be formulated as
     pharmaceutical compns.  They can be identified by appropriate screens.
RE.CNT  8
RE
(1) American Home Prod; EP 0778023 A 1997
(2) Ben-Eliyahu, S; PROCEEDINGS OF THE WESTERN PHARMACOLOGY SOCIETY 1993, V36,
    P293 HCAPLUS
(3) Chaudieu, I; J NEUROCHEM 1993, V61(suppl), PS255
(4) Igarashi, K; JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1995,
    V272(3), P1101 HCAPLUS
(6) Seiler, N; INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY 1998,
    V30(3), P393 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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=> d bib abs 123 3

L23  ANSWER 3 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   1999:722875  HCAPLUS
DN   131:341966
TI   Hemoglobin-haptoglobin complexes for hepatic drug delivery
IN   Adamson, J. Gordon; Wodzinska, Jolanta Maria; Moore, Marie Sylvie Celine
PA   Hemosol Inc., Can.
SO   PCT Int. Appl., 51 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   WO 9956723        A2   19991111      WO 1999-CA396    19990430
     WO 9956723        A3   20000106
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
             JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
             TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD,
             RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9936960        A1   19991123      AU 1999-36960    19990430
PRAI CA 1998-2236344   19980430
     WO 1999-CA396     19990430
AB   Construct-complexes of a Hb, a hepatocyte modifying substance
     bound to the Hb, and a haptoglobin bound to the Hb, are provided, for
     administration to mammalian patients.  The construct-complex may
     be formed ex vivo , or a Hb-hepatocyte modifying substance combination may
     be administered to the patient so that haptoglobin in the mammalian body
     bonds thereto to form the construct-complex in vivo .  Disorders
     of the liver may be diagnosed and treated using construct-
     complexes described herein.
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=> d bib abs l23 4

L23  ANSWER 4 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   1998:352961  HCAPLUS
DN   129:37202
TI   Novel polymeric complexes for the transfection of
     nucleic acids, with residues causing the destabilization of cell
     membranes
IN   Midoux, Patrick; Monsigny, Michel
PA   I.D.M. Immuno-Designed Molecules, Fr.; Midoux, Patrick; Monsigny, Michel
SO   PCT Int. Appl., 83 pp.
     CODEN: PIXXD2
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   WO 9822610         A1   19980528      WO 1997-FR2022   19971110
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
             US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     FR 2755976         A1   19980522      FR 1996-13990    19961115
     FR 2755976         B1   19990115
     AU 9851239         A1   19980610      AU 1998-51239    19971110
     EP 946744          A1   19991006      EP 1997-945903   19971110
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRAI FR 1996-13990    19961115
     WO 1997-FR2022   19971110
OS   MARPAT 129:37202
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AB The invention concerns a **complex** between at least a (neg. charged) **nucleic** acid and at least a pos. charged polymeric **conjugate,** the bond between the **nucleic** acid and the polymeric **conjugate** being electrostatic in nature, the polymeric **conjugate** contg. a polymer formed by monomer units bearing free NH3+ functions, and being such that: the free NH3+ functions of said monomer units are substituted in a ratio of .gtoreq.10 % by residues causing in weak acid medium destabilization of cell membranes, in particular the endocytosis vesicle membrane, and/or endosomes; said residues having further the following properties: they comprise a functional group for being fixed to said polymer, they are not active as recognition signal identified by a cell membrane receptor, they can comprise at least one free NH3+ function; said uncharged residues having further the following properties: they comprise at least a hydroxyl group, they are not active as recognition signal identified by a cell membrane receptor, the hydroxyl groups of said uncharged residues being capable of being substituted by at least a mol. which constitutes a recognition signal identified by a cell membrane receptor, with reservation that the whole set of free NH3+ functions is at least 30 % of the no. of monomer units of the polymeric network of said polymeric **conjugate**.

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=> d bib abs 123 5

L23  ANSWER 5 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   1998:147346  HCAPLUS
DN   128:213381
TI   Compositions and methods for treating infections using analogs of
     indolicidin
IN   Fraser, Janet R.; West, Michael H. P.; Krieger, Timothy J.; Taylor,
     Robert; Erfle, Douglas
PA   Micrologix Biotech, Inc., Can.; Fraser, Janet R.; West, Michael H. P.;
     Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas
SO   PCT Int. Appl., 130 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
PI   WO 9807745        A2   19980226      WO 1997-US14779  19970821
     WO 9807745        A3   19980709
         W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,
            EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,
            LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
            RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN,
            YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
            GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
            GN, ML, MR, NE, SN, TD, TG
     AU 9743279        A1   19980306      AU 1997-43279    19970821
     EP 925308         A2   19990630      EP 1997-941352   19970821
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, FI
PRAI US 1996-24754      19960821
     US 1997-34949      19970113
     US 1997-34849      19970113
     WO 1997-US14779    19970821
OS   MARPAT 128:213381
AB   Compns. and methods for treating infections, esp. bacterial infections,
     are provided.  Indolicidin peptide analogs contg. at least two basic amino
     acids are prepd.  The analogs are administered as modified peptides,
     preferably contg. photo-oxidized solubilizer.

=> d ind 5

L23  ANSWER 5 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
IC   ICM  C07K007-06
     ICS  C07K007-08; C07K014-00; C07K016-44; C12N015-11; A61K038-16;
          A61K038-08; A61K038-10; A61K047-48
CC   1-5 (Pharmacology)
     Section cross-reference(s): 34, 63
ST   indolicidin analog peptide prepn antiinfective antibacterial
IT   Streptococcus
        (Viridans-group; indolicidin analogs, and combinations with other
        agents, for treating infections)
IT   Alkaloids, biological studies
     RL: BAC (Biological activity or effector, except adverse); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (cinchonan; indolicidin analogs, and combinations with other agents,
        for treating infections)
IT   Proteins (specific proteins and subclasses)
     RL: BAC (Biological activity or effector, except adverse); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (conjugates, with polyoxyalkylene glycol and fatty acid;
        indolicidin analogs, and combinations with other agents, for treating
        infections)
IT   Fatty acids, biological studies
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Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates**; indolicidin analogs, and combinations with other agents, for treating infections)

IT Bacteria (Eubacteria)
(diphtheroid; indolicidin analogs, and combinations with other agents, for treating infections)

IT Liquid dosage forms (drug delivery systems)
(drops; indolicidin analogs, and combinations with other agents, for treating infections)

IT Drug delivery systems
(enteric; indolicidin analogs, and combinations with other agents, for treating infections)

IT Injections (drug delivery systems)
(i.p.; indolicidin analogs, and combinations with other agents, for treating infections)

IT Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analog **conjugates**; indolicidin analogs for treating infections)

IT Acinetobacter
Acinetobacter calcoaceticus
Adenoviridae
Alphavirus
Anaerobic bacteria
Anti-infective agents
Antibacterial agents
Antimalarials
Antimicrobial agents
Antiviral agents
Arenavirus
Ascaris lumbricoides
Babesia
Bacillus (bacterium genus)
Bactericidal structure-activity relationship
Bacteroides
Balantidium coli
Blastocystis hominis
Bordetella pertussis
Borrelia
Bovine leukemia virus
Brucella
Bunyavirus
Campylobacter
Chlamydia
Clonorchis sinensis
Clostridium
Coagulase-negative Staphylococcus
Coronavirus
Corynebacterium
Cryptosporidium parvum
Cytomegalovirus
Drug delivery systems
Echinococcus
Encephalitozoon
Entamoeba
Enterobacter
Enterobacter cloacae
Enterococcus faecalis
Enterococcus faecium
Enterovirus
Escherichia coli
Fasciola hepatica
Fasciolopsis buski
Filovirus
Flavivirus
Fungicides
Genetic **vectors**

Giardia lamblia
Gram-negative bacteria
Gram-positive bacteria (Firmicutes)
Haemophilus ducreyi
Haemophilus influenzae
Hantavirus
Helicobacter pylori
Hemolysis
Hepadnaviridae
Heterophyes heterophyes
Human T-lymphotropic virus
Hymenolepis
Implants (drug delivery systems)
Influenza virus
Inhalants (drug delivery systems)
Injections (drug delivery systems)
Intramuscular injections
Intravenous injections
Klebsiella pneumoniae
Legionella
Leishmania
Lentivirus
Liposomes (drug delivery systems)
Listeria
Lyssavirus
Medical goods
Mold (fungus)
Molecular structure
Molluscipoxvirus
Moraxella catarrhalis
Mycobacterium
Mycoplasma
Neisseria
Nematode (Nematoda)
Oral drug delivery systems
Orthopoxvirus
Papillomavirus
Paramyxovirus
Parasiticides
Parvovirus
Peptostreptococcus
Pharmacokinetics
Plasmodium (malarial genus)
Polyomavirus
Propionibacterium acnes
Protozoacides
Pseudomonas aeruginosa
RNA viruses
Reoviridae
Rhinovirus
Rickettsia
Rotavirus
Salmonella
Schistosoma
Serratia marcescens
Shigella
Simplexvirus
Sprays (drug delivery systems)
Staphylococcus aureus
Staphylococcus epidermidis
Stenotrophomonas maltophilia
Streptococcus pneumoniae
Streptococcus pyogenes
Subcutaneous injections
Suppositories (drug delivery systems)
Synergistic drug interactions
Taenia
Tapeworm (Cestoda)
Topical drug delivery systems
Toxicity

Toxoplasma gondii
Trematode (Trematoda)
Treponema
Trichinella
Trichomonas
Trypanosoma
Ureaplasma
Varicellovirus
Yeast
Yersinia
(indolicidin analogs, and combinations with other agents, for treating infections)

IT Aminoglycoside antibiotics
Antibiotics
Glycopeptides
Interferons
Macrolide antibiotics
Peptides, biological studies
Quinolone antibiotics
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT **Nucleic** acids
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT Antibodies
Monoclonal antibodies
Single chain antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT Nasal drug delivery systems
Sprays (drug delivery systems)
(nasal sprays; indolicidin analogs, and combinations with other agents, for treating infections)

IT Membranes (nonbiological)
(permeabilization; indolicidin analogs, and combinations with other agents, for treating infections)

IT UV radiation
(polyoxyalkylene glycol activation with; indolicidin analogs, and combinations with other agents, for treating infections)

IT Drug delivery systems
(slow-release; indolicidin analogs, and combinations with other agents, for treating infections)

IT Suppositories (drug delivery systems)
(vaginal; indolicidin analogs, and combinations with other agents, for treating infections)

IT Amino acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D-; indolicidin analogs, and combinations with other agents, for treating infections)

IT 140896-21-5D, Indolicidin, analogs 204244-86-0 204244-86-0D, branched peptide and other derivs. 204244-87-1 204244-87-1D, branched peptide and other derivs. 204244-88-2 204244-88-2D, branched peptide and other derivs. 204244-89-3 204244-89-3D, branched peptide and other derivs.
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204246-70-8 204246-71-9 204246-72-0 204246-73-1 204246-74-2
RL: BAC (Biological activity or effector, except adverse); DEV (Device component use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs for treating infections)

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RL: BAC (Biological activity or effector, except adverse); DEV (Device component use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs for treating infections)

IT 204249-51-4 204249-52-5 204249-53-6 204249-54-7 204249-55-8
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RL: BAC (Biological activity or effector, except adverse); DEV (Device component use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs for treating infections)

IT 25322-68-3D, indolicidin analog **conjugates**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs for treating infections)

IT 140896-21-5, Indolicidin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT 204250-85-1D, **conjugates** with polyalkylene glycol and fatty acid
204250-86-2D, **conjugates** with polyalkylene glycol and fatty acid
204250-87-3D, **conjugates** with polyalkylene glycol and fatty acid
204250-88-4D, **conjugates** with polyalkylene glycol and fatty acid 204250-89-5D, **conjugates** with polyalkylene glycol and fatty acid 204250-90-8D, **conjugates** with polyalkylene glycol and fatty acid 204250-91-9D, **conjugates** with polyalkylene glycol and fatty acid 204250-92-0D, **conjugates** with polyalkylene glycol and fatty acid 204250-93-1D, **conjugates** with polyalkylene glycol and fatty acid 204250-94-2D, **conjugates** with polyalkylene glycol and fatty acid
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT 9005-65-6DP, Polysorbate 80, activated, **conjugates**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT 50-63-5, Chloroquine phosphate 50-65-7, Niclosamide 54-42-2, Idoxuridine 54-85-3, Isoniazid 54-85-3D, Isoniazid, derivs. 56-75-7, Chloramphenicol 56-75-7D, Chloramphenicol, derivs. 57-92-1, Streptomycin, biological studies 57-92-1D, Streptomycin, derivs. 58-14-0, Pyrimethamine 60-54-8, Tetracycline 60-54-8D, Tetracycline, derivs. 61-32-5, Methicillin 61-32-5D, Methicillin, derivs. 61-33-6, Penicillin G, biological studies 61-33-6D, Penicillin G, derivs. 61-72-3, Cloxacillin 61-72-3D, Cloxacillin, derivs. **63-45-6**, Primaquine phosphate 66-79-5, Oxacillin 66-79-5D, Oxacillin, derivs. 67-20-9, Nitrofurantoin 67-20-9D, Nitrofurantoin, derivs. 69-53-4, Ampicillin 69-53-4D, Ampicillin, derivs. 70-00-8, Trifluridine 74-55-5, Ethambutol 74-55-5D, Ethambutol, derivs. 83-73-8, Iodoquinol 91-22-5D, Quinoline, derivs. 98-96-4, Pyrazinamide 98-96-4D, Pyrazinamide, derivs. 104-29-0, Chlorphenesin 107-11-9D, Allylamine, derivs. 110-85-0, Piperazine, biological studies 110-85-0D, Piperazine, derivs. 112-38-9, 10-Undecenoic acid 114-07-8, Erythromycin 114-07-8D, Erythromycin, derivs. 126-07-8, Griseofulvin 130-26-7, Clioquinol 140-64-7, Pentamidine isethionate 145-63-1, Suramin 147-52-4, Nafcillin 147-52-4D, Nafcillin, derivs. 148-24-3D, 8-Hydroxyquinoline, derivs. 148-79-8, Thiabendazole 153-61-7, Cephalothin 153-61-7D, Cephalothin, derivs. 288-32-4D, Imidazole, derivs. 289-95-2D, Pyrimidine, derivs. 389-08-2, Nalidixic acid

389-08-2D, Nalidixic acid, derivs. 443-48-1, Metronidazole 443-48-1D, Metronidazole, derivs. 494-79-1 500-92-5, Proguanil 518-28-5, Podophyllotoxin 564-25-0, Doxycycline 564-25-0D, Doxycycline, derivs. 643-22-1, Erythromycin stearate 643-22-1D, Erythromycin stearate, derivs. 665-66-7, Amantadine hydrochloride 723-46-6, Sulfamethoxazole 723-46-6D, Sulfamethoxazole, derivs. 738-70-5 738-70-5D, derivs. 804-63-7, Quinine sulfate 1264-62-6, Erythromycin ethyl succinate 1264-62-6D, Erythromycin ethyl succinate, derivs. 1397-89-3, Amphotericin B 1400-61-9, Nystatin 1403-66-3, Gentamicin 1403-66-3D, Gentamicin, derivs. 1404-90-6, Vancomycin 1404-90-6D, Vancomycin, derivs. 1406-05-9, Penicillin 1642-54-2, Diethyl carbamazine citrate 2022-85-7, 5-Fluorocytosine 2398-96-1, Tolnaftate 3056-17-5, Stavudine 3116-76-5, Dicloxacillin 3116-76-5D, Dicloxacillin, derivs. 3521-62-8, Erythromycin estolate 3521-62-8D, Erythromycin estolate, derivs. 3546-41-6, Pyrvinium pamoate 3847-29-8, Erythromycin lactobionate 3847-29-8D, Erythromycin lactobionate, derivs. 4428-95-9, Foscarnet 4697-36-3, Carbenicillin 4697-36-3D, Carbenicillin, derivs. 5536-17-4, Vidarabine 7054-25-3, Quinidine gluconate 7481-89-2, Zalcitabine 7542-37-2, Paromomycin 8063-07-8, Kanamycin 8063-07-8D, Kanamycin, derivs. 9005-64-5D, **conjugates** 11111-12-9, Cephalosporin 12441-09-7D, Sorbitan, reaction products with polyoxyalkylene glycol and fatty acid, **conjugates** 12650-69-0, Mupirocin 12650-69-0D, Mupirocin, derivs. 13292-46-1, Rifampicin 13292-46-1D, Rifampicin, derivs. 13392-28-4, Rimantadine 13614-98-7, Minocycline hydrochloride 13614-98-7D, Minocycline hydrochloride, derivs. 15176-29-1, Edoxudine 15686-71-2, Cephalexin 15686-71-2D, Cephalexin, derivs. 16037-91-5, Sodium stibogluconate 18323-44-9, Clindamycin 18323-44-9D, Clindamycin, derivs. 22204-24-6, Pyrantel pamoate 22916-47-8, Miconazole 23067-13-2, Erythromycin glucoheptonate 23067-13-2D, Erythromycin glucoheptonate, derivs. 23256-30-6, Nifurtimox 23593-75-1, Clotrimazole 25953-19-9, Cefazolin 25953-19-9D, Cefazolin, derivs. 26787-78-0, Amoxicillin 26787-78-0D, Amoxicillin, derivs. 27220-47-9, Econazole 28657-80-9, Cinoxacin 28657-80-9D, Cinoxacin, derivs. 29342-05-0, Ciclopirox 30516-87-1, Zidovudine 31431-39-7, Mebendazole 32986-56-4, Tobramycin 32986-56-4D, Tobramycin, derivs. 34787-01-4, Ticarcillin 34787-01-4D, Ticarcillin, derivs. 35607-66-0, Cefoxitin 35607-66-0D, Cefoxitin, derivs. 36791-04-5, Ribavirin 36877-68-6D, Nitroimidazole, derivs. 37091-66-0, Azlocillin 37091-66-0D, Azlocillin, derivs. 37231-28-0D, Melittin, cecropin fusion products 37306-44-8D, Triazole, derivs. 37517-28-5, Amikacin 37517-28-5D, Amikacin, derivs. 39809-25-1, Penciclovir 42540-40-9, Cefamandole formate sodium 42540-40-9D, Cefamandole formate sodium, derivs. 51481-65-3, Mezlocillin 51481-65-3D, Mezlocillin, derivs. 51773-92-3, Mefloquine hydrochloride 53994-73-3, Cefaclor 53994-73-3D, Cefaclor, derivs. 54965-21-8, Albendazole 55268-74-1, Praziquantel 55268-75-2, Cefuroxime 55268-75-2D, Cefuroxime, derivs. 56093-45-9, Selenium sulfide 56391-56-1, Netilmicin 56391-56-1D, Netilmicin, derivs. 56796-20-4, Cefmetazole 56796-20-4D, Cefmetazole, derivs. 59277-89-3, Acyclovir 61036-62-2, Teicoplanin 61036-62-2D, Teicoplanin, derivs. 61270-58-4, Cefonicid 61270-58-4D, Cefonicid, derivs. 61318-90-9, Sulconazole 61477-96-1, Piperacillin 61477-96-1D, Piperacillin, derivs. 62587-73-9, Cefsulodin 62587-73-9D, Cefsulodin, derivs. 62893-19-0, Cefoperazone 62893-19-0D, Cefoperazone, derivs. 63527-52-6 63527-52-6D, derivs. 63744-80-9, Cephamycin 64221-86-9, Imipenem 64221-86-9D, Imipenem, derivs. 64872-76-0, Butoconazole 65052-63-3, Cefetamet 65052-63-3D, Cefetamet, derivs. 65277-42-1, Ketoconazole 65473-14-5, Naftifine hydrochloride 65899-73-2, Tioconazole 67915-31-5, Terconazole 68401-81-0, Ceftizoxime 68401-81-0D, Ceftizoxime, derivs. 69655-05-6, Didanosine 69712-56-7, Cefotetan 69712-56-7D, Cefotetan, derivs. 69756-53-2, Halofantrine 70052-12-9, Eflornithine 70288-86-7, Ivermectin 70458-96-7, Norfloxacin 70458-96-7D, Norfloxacin, derivs. 72558-82-8, Ceftazidime 72558-82-8D, Ceftazidime, derivs. 72559-06-9, Rifabutin 72559-06-9D, Rifabutin, derivs. 73384-59-5, Ceftriaxone 73384-59-5D, Ceftriaxone, derivs. 74011-58-8, Enoxacin 74011-58-8D, Enoxacin, derivs. 76470-66-1, Loracarbef 76470-66-1D, Loracarbef, derivs. 77181-69-2, Sorivudine 78110-38-0, Monobactam 78110-38-0D, Aztreonam, derivs. 78628-80-5, Terbinafine hydrochloride 79198-29-1 79198-29-1D, derivs. 79350-37-1, Cefixime 79350-37-1D, Cefixime, derivs. 79660-72-3, Fleroxacin 79660-72-3D, Fleroxacin, derivs.

80210-62-4, Cefpodoxime 80210-62-4D, Cefpodoxime, derivs. 80214-83-1, Roxithromycin 80214-83-1D, Roxithromycin, derivs. 80802-79-5D, Cecropin, mellitin fusion products 81103-11-9, Clarithromycin 81103-11-9D, Clarithromycin, derivs. 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82419-36-1D, Ofloxacin, derivs. 83200-96-8, Carbapenem 83905-01-5, Azithromycin 83905-01-5D, Azithromycin, derivs. 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 85721-33-1D, Ciprofloxacin, derivs. 86386-73-4, Fluconazole 88040-23-7, Cefepime 88040-23-7D, Cefepime, derivs. 92665-29-7, Cefprozil 92665-29-7D, Cefprozil, derivs. 95233-18-4, Atovaquone 96036-03-2, Meropenem
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

IT 96036-03-2D, Meropenem, derivs. 98079-51-7, Lomefloxacin 98079-51-7D, Lomefloxacin, derivs. 104227-87-4, Famciclovir 123683-33-0, Piperacillin-tazobactam-mixt. 123683-33-0D, Piperacillin-tazobactam-mixt., derivs. 126602-89-9, Synercid 126602-89-9D, Synercid, derivs. 129618-40-2, Nevirapine 134678-17-4, Lamivudine 204250-85-1 204250-86-2 204250-87-3 204250-88-4 204250-89-5 204250-90-8 204250-91-9 204250-92-0 204250-93-1 204250-94-2
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolicidin analogs, and combinations with other agents, for treating infections)

=> d bib abs l23 6

L23 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:317957 HCAPLUS
DN 125:27149
TI Putative role of chloroquine in gene transfer into a human hepatoma cell line by **DNA**/lactosylated polylysine **complexes**
AU Erbacher, Patrick; Roche, Annie Claude; Monsigny, Michel; Midoux, Patrick
CS Centre Biophysique Moleculaire, CNRS Univ. d'Orleans, Orleans, F-45071, Fr.
SO Exp. Cell Res. (1996), 225(1), 186-194
CODEN: ECREAL; ISSN: 0014-4827
DT Journal
LA English
AB Chloroquine improves drastically the transfection of cells upon exposure to **plasmid DNA**/glycosylated polylysine **complexes**. So far the mechanism of action of chloroquine is not well understood. In this paper, the effect of chloroquine was investigated by measuring the transfection efficiency of a human hepatocarcinoma (HepG2 cells) by pSV2LUC/lactosylated polylysine **complexes** involving their internalization via the galactose-specific membrane lectin of these cells. The luciferase activity in the transfected cells was maximal when the transfection was performed for 3 or 4 h in the presence of 100 .mu.M chloroquine. The luciferase activity was also enhanced in the presence of primaquine, a chloroquine analog, but was not increased when transfection was performed in the presence of ammonium chloride, methylamine, spermine, or monensin, compds. known to neutralize the pH of the endocytotic vesicle lumen as chloroquine does. Chloroquine enters cells and accumulates in vesicular compartments; the overall intracellular concn. increases to 9 mM, which means that in the vesicular compartment, the chloroquine concns. is still higher. At such high concns., chloroquine induces the dissocn. of **plasmid DNA**/lactosylated polylysine **complexes**, as shown in a cellular expts.

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=> d bib abs l23 7

L23  ANSWER 7 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   1995:982331  HCAPLUS
DN   124:4497
TI   Heterocyclic chemiluminescent derivatives
IN   Renotte, Roger Remy; Sarlet, Guy Nicolas; Lejeune, Robert Ghislain
PA   Biocode S. A., Belg.
SO   PCT Int. Appl., 93 pp.
     CODEN: PIXXD2
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   WO 9519976         A1   19950727      WO 1995-BE7      19950125
         W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG,
             KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO,
             RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN
         RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU,
             MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN,
             TD, TG
     BE 1008216         A4   19960220      BE 1994-87       19940125
     AU 9515292         A1   19950808      AU 1995-15292    19950125
     EP 741720          A1   19961113      EP 1995-906853   19950125
         R: BE, DE, ES, FR, GB, IT
PRAI BE 1994-87         19940125
     WO 1995-BE7        19950125
OS   MARPAT 124:4497
AB   The prepn. and anal. use are disclosed of heterocyclic chemiluminescent
     derivs. of acridinium (and substituted derivs. thereof), phenanthridinium
     (and substituted derivs. thereof), quinolinium (and substituted derivs.
     thereof) and isoquinolinium (and substituted derivs. thereof).  The
     compds. may be used to label biol. mols., e.g., antibodies, for use in the
     detection or detn. of, e.g., antigens, and an example is given of the
     detn. of TSH in blood serum by an immunoassay using an antibody labeled
     with one such deriv.
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=> d bib abs 123 8

L23 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:446547 HCAPLUS
DN 117:46547
TI Human immunodeficiency virus (HIV) principal neutralizing determinant peptides and **conjugates** for vaccine
IN Lewis, John A.; Davide, Joseph P.; Waterbury, Julie Ann
PA Merck and Co., Inc., USA
SO Eur. Pat. Appl., 177 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 471407	A2	19920219	EP 1991-202025	19910807
	EP 471407	A3	19930512		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	CA 2048594	AA	19920214	CA 1991-2048594	19910807
	NO 9103127	A	19920214	NO 1991-3127	19910812
	FI 9103817	A	19920214	FI 1991-3817	19910812
	AU 9181777	A1	19920220	AU 1991-81777	19910812
	AU 642751	B2	19931028		
	ZA 9106344	A	19920429	ZA 1991-6344	19910812
	JP 06321808	A2	19941122	JP 1991-202789	19910813
PRAI	US 1990-566638	19900813			
	US 1990-566654	19900813			
	US 1990-566656	19900813			

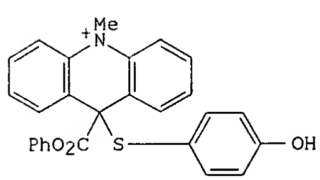
AB Envelope fragment peptide fragments of HIV are provided, as are **conjugates** of the peptides with purified outer membrane proteosome (omp) of Neisseria. The peptide **conjugates** are useful for vaccinating against AIDS or AIDS-related **complex**. Amino acid sequences (and corresponding nucleotide sequences) for the peptides are included. Polymerase chain reaction (PCR) amplification of genomic **DNA** from HIV isolates, cloning of the PCR-amplified **DNA**, and sequence detn. are described, as is extn. and purifn. of the Neisseria meningitidis omp. Also described is anal. of sera for anti-peptide IgG and for HIV infectivity-neutralizing activity (no data).

=> d bib abs l23 9

L23 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:511982 HCAPLUS
DN 113:111982
TI Protected chemiluminescent labels
IN Arnold, Lyle John; Waldrop, Alexander Atkinson, III; Hammond, Philip W.
PA Gen-Probe, Inc., USA
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 330433	A2	19890830	EP 1989-301679	19890222
	EP 330433	A3	19910227		
	EP 330433	B1	19960417		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 4950613	A	19900821	US 1988-160611	19880226
	AT 137021	E	19960515	AT 1989-301679	19890222
	ES 2012323	T3	19960616	ES 1989-301679	19890222
	CA 1333396	A1	19941206	CA 1989-591999	19890224
	WO 8908256	A1	19890908	WO 1989-US722	19890227
	W: AU, DK, FI, JP, KR, NO				
	AU 8940723	A1	19890922	AU 1989-40723	19890227
	AU 626319	B2	19920730		
	JP 02503268	T2	19901011	JP 1989-503114	19890227
	NO 8904218	A	19891222	NO 1989-4218	19891024
	DK 8905304	A	19891227	DK 1989-5304	19891025

PRAI US 1988-160611 19880226
WO 1989-US722 19890227
OS MARPAT 113:111982
GI



I

AB A chemiluminescent label (e.g. an acridan, acridinium, or quinolinium compd.), for use in a specific binding assay, is protected from inactivation during storage or incubation of the labeled reagent with the analyte by formation of a protective adduct. Thus, an **oligonucleotide** labeled with an acridinium Ph ester was protected from heat and long hybridization times by formation of adduct I with 4-hydroxythiophenol, as shown by a 3-fold increase light signal compared to the unprotected compd.

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=> d bib abs l23 10

L23  ANSWER 10 OF 22  HCAPLUS  COPYRIGHT 2000 ACS
AN   1989:619278  HCAPLUS
DN   111:219278
TI   Poly(lactide)-containing microspheres containing primaquine for the
     treatment of malaria
IN   Bontemps, Jose; Pirson, Philippe; Falmagne, Jean Bernard; Jerome, Robert;
     Teyssie, Philippe; Delattre, Luc; Evrard, Brigitte
PA   IRE-Celltarg S. A., Belg.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
DT   Patent
LA   French
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.   DATE
     ---------------  ----  --------      ---------------   --------
PI   EP 301969         A1   19890201      EP 1988-401965    19880728
     EP 301969         B1   19910821
         R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
     FR 2618674        A1   19890203      FR 1987-10802     19870730
     FR 2618674        B1   19900615
     AT 66372          E    19910915      AT 1988-401965    19880728
     CA 1329549        A1   19940517      CA 1988-573303    19880728
     JP 01042433       A2   19890214      JP 1988-188520    19880729
PRAI FR 1987-10802     19870730
     EP 1988-401965    19880728
OS   MARPAT 111:219278
AB   Microparticles comprise microspheres consisting of poly(lactide),
     preferably in the DL-form, which contain an active agent which is
     primaquine or its derivs. PQ-X (PQ = primaquine; X = amino acid, peptide
     with 1-4 amino acids; the PQ-X bond is a covalent peptide bond between the
     free amine group of primaquine and the carboxyl group of X), or a
     conjugate of primaquine or a deriv. of primaquine with a
     hepatotropic vector, and their salts.  A dispersion contg. 2.7 g
     poly(DL-lactide), 23 mL Me2CO, 0.83 g Span-80, and 0.7 g primaquine
     diphosphate was sonicated and emulsified at 0.degree. while adding a
     suspension of liq. paraffin in Me2CO and subsequently the solvent was
     removed slowly by evapn. and the microspheres were recovered; rapid evapn.
     of solvent gave hollow and even ruptured microspheres.  In order to reduce
     the size of the microspheres in the paraffin-Me2CO system using sorbitan
     esters, the latter are present at 1-10% by wt.  The emulsification
     conditions are also crit.; agitation at 800 rotations per min. yielded
     microspheres with a particle size <200 .mu.m.  Using microspheres with a
     particle size of 160-200 .mu.m, the amt. of active agent released in
     isotonic phosphate buffer within the 1st h was 0%, within the 1st day
     8.0%, and the microspheres did not show a burst effect and the release was
     of zero order.  Prior to infection with Plasmodium berghei sporozoites
     mice were treated with a compn. contg. the above sample compn. and a 36
     mg/kg daily dose of primaquine gave partial protection and a 50 mg/kg
     daily dose gave complete protection and the optimal treatment time of
     murine malaria was 14 days.  N-Glutamylprimaquine was prepd. and also
     encapsulated in poly(DL-lactide).
```

=> d bib abs 123 11

L23 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:94360 HCAPLUS
Correction of: 1988:509706
DN 110:94360
Correction of: 109:109706
TI Triplet-triplet absorption spectra of organic molecules in condensed phases.
AU Carmichael, Ian; Hug, Gordon L.
CS Radiat. Chem. Data Cent., Univ. Notre Dame, Notre Dame, IN, 46556, USA
SO J. Phys. Chem. Ref. Data (1986), 15(1), 1-250
CODEN: JPCRBU; ISSN: 0047-2689
DT Journal
LA English
AB A review in which a compilation is given of spectral parameters assocd. with triplet-triplet absorption of org. mols. in condensed media. The wavelengths of max. absorbance and the corresponding extinction coeffs., where known, were critically evaluated. Other data, for example, lifetimes, energies, and energy transfer rates, relevant to the triplet states of these mols., are included by way of comments, but have not been subjected to a similar scrutiny. An introduction is given to triplet state processes in soln. and solids, developing the conceptual background and offering a historical perspective on the detection and measurement of triplet state absorption. Techniques employed to populate the triplet state are reviewed and the various approaches to the estn. of the extinction coeff. of tripley-triplet absorption are discussed. A statistical anal. of the available data is presented and recommendations for a hierarchical choice of extinction coeffs. are made. Data collection is expected to be complete through the end of 1984.

=> d bib abs 123 12

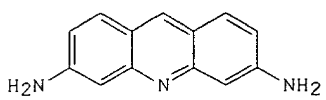
L23 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:509706 HCAPLUS
Correction of: 1986:552243
DN 109:109706
Correction of: 105:152243
TI Triplet-triplet absorption spectra of organic molecules in condensed phases
AU Carmichael, Ian; Hug, Gordon L.
CS Radiat. Chem. Data Cent., Univ. Notre Dame, Notre Dame, IN, 46556, USA
SO J. Phys. Chem. Ref. Data (1986), 15(1), 1-250
CODEN: JPCRBU; ISSN: 0047-2689
DT Journal; General Review
LA English
AB A review in which a compilation is given of spectral parameters assocd. with triplet-triplet absorption of org. mols. in condensed media. Other data, for example, lifetimes, energies and energy transfer rates, relevant to the triplet states of these mols., are included by way of comments, but have not been subjected to a similar scrutiny. An introduction is given to triplet state processes in soln. and solids, developing the conceptual background and offering an historical perspective on the detection and measurement of triplet state absorption. Techniques employed to populate the triplet state are reviewed and the various approaches to the estn. of the extinction coeff. of triplet-triplet absorption are discussed. A statistical anal. of the available data is presented and recommendations for a hierarchical choice of extinction coeffs. are made. Data collection is expected to be complete through the end of 1984.

=> d bib abs 123 13

L23 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1980:400465 HCAPLUS
DN 93:465
TI Inhibition of hepatitis B virus specific **DNA** polymerase by intercalating agents
AU Hess, G.; Arnold, W.; Moeller, B.; Gahl, G. M.; Meyer, K. H.
CS Dep. Intern. Med., Freie Univ. Berlin, Berlin, D-1000/19, Fed. Rep. Ger.
SO Med. Microbiol. Immunol. (1980), 168(1), 25-34
CODEN: MMIYAO; ISSN: 0300-8584
DT Journal
LA English
AB Of 6 intercalating agents tested for their ability to inhibit the hepatitis B virus specific **DNA** polymerase [9012-90-2] reaction, ethidium bromide [1239-45-8] was the strongest inhibitor. The remaining compds. inhibited the **DNA** polymerase only at high concns. The inhibitory activity of all compds. tested was increased when the MgCl2 content in the reaction mixt. was lowered. UV absorption studies presented no evidence that this effect was due to **complex** formation of Mg2+ and the individual compds. The therapeutic significance of these findings is not certain.

=> d bib abs l23 14

L23 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:587457 HCAPLUS
DN 91:187457
TI Mechanism of enhancement of **polynucleotide** binding to cells by mutagens
AU Noronha-Blob, Lalita; Pitha, Josef
CS Natl. Inst. Aging, NIH, Baltimore, MD, 21224, USA
SO Biochemistry (1979), 18(15), 3206-9
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
GI



I

AB The binding of polyuridylate [27416-86-0] to fibroblast cells was substantially increased by proflavine (I) [92-62-6]. This enhanced binding was saturable with respect to time and to the concn. of both I and polyuridylate. Enhancement was obsd. only when cells were exposed to both I and polyuridylate together and depended cooperatively on the I concn. The resulting **complex** formed between the cell, I, and polyuridylate could be dissocd. with salt but not with sucrose solns. An increase in the binding of polyuridylate to cells similar to that obsd. with I was also obtained with cationic dyes such as acridine orange [65-61-2], 9-aminoacridine [90-45-9], and Hoechst 33258 [23491-45-4], while the introduction of a bulky polysaccharide residue, dextran, into the dyes cancelled these effects. Similarly, cationic arom. compds. such as primaquine [**90-34-6**] and quinacrine [83-89-6] which carry bulky nonplanar substituents or aliph. cationic compds. like ethylenediamine [107-15-3] did not enhance binding. I was unable to augment the binding of a basic macromol., diethylaminoethyldextran [9015-73-0], to cells. The model proposed for the enhanced binding of polyuridylate was based on the cooperative formation of stacked **complexes** of cationic dye located between the cell surface and the bound polyuridylate.

=> d ind 14

L23 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2000 ACS
CC 4-3 (Toxicology)
Section cross-reference(s): 1
ST polyuridylate binding fibroblast mutagen
IT Mutagens
(polyuridylate binding to fibroblasts response to)
IT Fibroblast
(polyuridylate binding to, mutagens effect on)
IT 27416-86-0
RL: BIOL (Biological study)
(binding of, to fibroblasts, mutagens effect on)
IT 65-61-2 90-45-9 92-62-6 23491-45-4
RL: BIOL (Biological study)
(polyuridylate binding to fibroblasts enhancement by)
IT 83-89-6 **90-34-6** 107-15-3, biological studies 9004-54-0D, oxidized, reduced aryl Schiff bases 9015-73-0
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(polyuridylate binding to fibroblasts response to)

=> d bib abs l23 15

L23 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:71150 HCAPLUS
DN 88:71150
TI Reagents specific for cell surface components
AU Pitha, Josef
CS Natl. Inst. Aging, NIH, Baltimore, Md., USA
SO Eur. J. Biochem. (1978), 82(1), 285-92
CODEN: EJBCAI
DT Journal
LA English
AB Hg, diazonium ions, and dyes that bind **nucleic** acids were covalently linked to dextrans by using methods that resulted in nonhydrolyzable reagent-dextran bonds without impairing the binding abilities of the reagents; i.e., these dextran derivs. reacted with thiols, phenols or imidazoles, and **nucleic** acids, resp. Since these dextran derivs. cannot penetrate into cells and since dextran itself does not bind to cells, these compds. represent reagents specific for the cell surface. They may be used both to evaluate cell surface constituents of intact cells and to affect viable cells via an interaction with those constituents. Hg-dextran (I) bound to cells; the amt. of Hg thus attached to the cells was .apprx.10 times smaller than when an equiv. concn. of free Hg2+ was used. I, bound to cells after a 30-min exposure at room temp., was localized on the surface of these cells, as NaBH4 reduced this **complex** giving rise to the intact cells, elementary Hg, and free dextran which was released into medium. When cells were constantly exposed to I, its toxic effects were comparable to that of Hg2+. Diazonium-dextran, which also binds tightly to the cell surface, also was quite toxic. Dextrans substituted with dyes which bind to **nucleic** acids were less toxic than the parent dyes themselves; the attachment of such a dye to dextran decreased the binding of dye to cells under detection limits.

=> d ind 15

L23 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2000 ACS
CC 9-13 (Biochemical Methods)
ST cell membrane labeling dextran deriv; mercury dextran cell label; diazonium dextran cell; nucleate dye cell deriv label
IT **Nucleic** acids
Phenols, reactions
Thiols, reactions
RL: ANST (Analytical study)
(labeling of, on cell surface with dextran derivs.)
IT Cell membrane
(surface, labeling of, with diazonium- and dye- and mercury-dextran derivs.)
IT Leukemia
(erythro-, dextran derivs. labeling of cell components of)
IT 9004-54-0, reactions
RL: RCT (Reactant)
(cell surface component labeling with reagents contg.)
IT 62-53-3DP, dextran derivs. 65-61-2DP, dextran derivs. **90-34-6DP**
, dextran derivs. 92-62-6DP, dextran derivs. 23491-45-4DP, dextran derivs.
RL: PREP (Preparation)
(prepn. of, as cell surface labeling reagent)
IT 9004-54-0DP, diazonium and dye and mercury derivs.
RL: PREP (Preparation)
(prepn. of, as cell surface labeling reagents)
IT 101-77-9 106-92-3 1600-27-7
RL: RCT (Reactant)
(reaction of, with dextran in cell surface labeling reagent prepn.)

=> d bib abs l23 16

L23 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:55426 HCAPLUS
DN 84:55426
TI Methyl green-**DNA complex** and its dissociation by drugs
AU Krey, Anne K.; Hahn, Fred E.
CS Dep. Mol. Biol., Walter Reed Army Inst. Res., Washington, D. C., USA
SO Biochemistry (1975), 14(23), 5061-7
CODEN: BICHAW
DT Journal
LA English
AB Spectrophotometric results indicated that Methyl Green (I) bound stably to native calf thymus **DNA** and to poly[d(A-T)] but to a lesser extent to .phi.X 174 **DNA**, tRNAs, and poly(dG.cntdot.dC), a copolymer that exists preferentially in the A conformation. Exposing the I-**DNA complex** to graded concns. of EtOH liberated part of the dye slowly by a zero-order reaction; higher EtOH concns. which cause the B .fwdarw. A transition of **DNA** released the bulk of I. The viscosity of the I-**DNA complex** was significantly lower than that of the uncomplexed **DNA**. The dye was progressively liberated from **DNA** by 1.5 .times. 10-1M NaCl and by much lower concns. of Mg2+; in its stoichiometric **complex** with **DNA**, it increased Tm by .apprx.12.degree.. A series of **DNA-complexing** drugs displaced I from **DNA** at exponential rates and to end points which were correlated. End points of displacement correlated with the abilities of drugs to unwind supercoiled **DNA**, to labilize ribosomes to heat, and to eliminate a kanamycin resistance determinant from an R factor carried by Salmonella typhimurium. Addnl. correlations between I displacement and biochem.-biol. activities of displacing drugs are cited. In conjunction with these findings, the results suggest that I displacement anal. is a useful biochem. screen for the detection or development of biol. active compds. which bind to **DNA**. It was concluded that I did not bind to **DNA** by intercalation, that I bound to double helices in their B conformation, and that the binding forces were predominantly electrostatic.

=> d ind 16

L23 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2000 ACS
CC 6-2 (General Biochemistry)
ST **DNA** dye **complex** dissocn drug; Methyl Green **DNA complex**
IT Deoxyribonucleic acids
RL: BIOL (Biological study)
(Methyl Green **complex**, dissocn. of, drug effect on)
IT Benzenaminium, 4-[[4-(dimethylamino)phenyl][4-(dimethyliminio)-2,5-cyclohexadien-1-ylidene]methyl]-N,N,N-trimethyl-, dichloride, **DNA complex**
RL: BIOL (Biological study)
(dissocn. of, drug effect on)
IT 50-76-0 54-05-7 64-17-5, biological studies 65-61-2 81-81-2
83-89-6 **90-34-6** 92-62-6 130-95-0 548-57-2 636-47-5
1239-45-8 2086-83-1 6035-39-8 12645-44-2 23257-53-6 23491-45-4
23541-50-6 25535-16-4 27591-69-1 37187-85-2 57514-27-9
58046-33-6 58046-34-7
RL: BIOL (Biological study)
(**DNA**-dye **complex** response to)

=> d bib abs l23 17

L23 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1974:512348 HCAPLUS
DN 81:112348
TI Dimeric structure of a **complex** in quinolinium tetrachloronitrosoplatoate crystals
AU Khodashova, T. S.; Sergienko, V. S.; Stetsenko, A. I.; Porai-Koshits, M. A.; Butman, L. A.
CS Inst. Obshch. Neorg. Khim. im. Kurnakova, Moscow, USSR
SO Zh. Strukt. Khim. (1974), 15(3), 471-7
CODEN: ZSTKAI
DT Journal
LA Russian
AB Based on x-ray structural anal., the title compd. (I), (C9H7)[PtNOCl4], contg. a 5-coordinative **complex** of [PtNOCl4]-, is triclinic, space group P1.**vector**., with lattice parameters a 8.103, b 10.687, c 8.772 .ANG., .alpha. 113.04, .beta. 93.3, .gamma. 77.21.degree.; Z = 2; R = 0.101. The crystals consist of centrosym. dimeric **complexes** of [Pt2(NO)2Cl8]2- and quinolinium ions. The coordination of Pt atoms forms a distorted octahedron. The Pt-N-O group is nonlinear (angle 112.degree.) and the Pt-N(NO) distance of 2.1-2.2 .ANG. is longer than that for M:N multiple bonds typical of **complexes** with linear M-N-O groups. A strong structural trans-effect of the nitroso group was detected.

=> d bib abs 123 18

L23 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1973:400090 HCAPLUS
DN 79:90
TI Binding of antimalarial aminoquinolines to chromatin, reconstituted deoxyribonucleohistone, and ribosomes from mammalian tissues
AU Washington, Mildred E.; White, Lidia A.; Holbrook, David J., Jr.
CS Sch. Med., Univ. North Carolina, Chapel Hill, N. C., USA
SO Biochem. Pharmacol. (1973), 22(4), 477-84
CODEN: BCPCA6
DT Journal
LA English
AB A study was conducted at low ionic strengths of the binding of primaquine [**90-34-6**], pentaquine [86-78-2], or chloroquine (I) [54-05-7] to **DNA**, to various **DNA**-protein **complexes** (chromatin isolated from calf thymus and reconstituted deoxyribonucleohistone prepns.), and to ribosomes isolated from rat liver. The order of binding to any of the nucleoproteins was chloroquine > pentaquine > primaquine. No binding of the aminoquinolines to free calf thymus histones was detected. For any of the 3 aminoquinolines, the greatest level of binding occurred to free **DNA** and to deoxyribonucleohistone contg. 0.5 mg histone/mg **DNA**, an intermediate level of binding to deoxyribonucleohistone contg. 1.00 or 1.2 mg histone/mg **DNA**, and the lowest level of binding to isolated chromatin. The decrease in binding of the aminoquinolines obsd. with increasing protein content of the polymers is due mainly to a decrease in the no. of potential binding sites and is also attributable to a small decrease in the strength of the binding.

=> d bib abs 123 19

L23 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:470701 HCAPLUS
DN 77:70701
TI Interaction of antimalarial aminoquinolines (primaquine, pentaquine, and chloroquine) with **nucleic** acids, and effects on various enzymic reactions in vitro
AU Holbrook, David J., Jr.; Whichard, Leona P.; Morris, Carl R.; White, Lidia A.
CS Sch. Med., Univ. North Carolina, Chapel Hill, N. C., USA
SO Progr. Mol. Subcell. Biol. (1971), 2, 113-25
CODEN: PMSBA4
DT Journal
LA English
AB The interaction of antimalarial 8-aminoquinolines with **DNA**, RNA, and various **polynucleotides** could be demonstrated by equil. dialysis and by direct spectrophotometry. Although appreciable binding of pentaquine (I) [86-78-2] and primaquine [**90-34-6**] occurred, the binding did not cause a significant change in the transition temp. or the viscosity of native **DNA**; the antimalarial 4-aminoquinoline, chloroquine [54-05-7] induced marked changes in both properties upon binding to native **DNA**. I and primaquine, and chloroquine inhibited the activity of Escherichia coil RNA polymerase [9014-24-8] assayed with calf thymus native **DNA** template in a medium contg. 1 mM Mn [7439-96-5] ions. The **DNA**-aminoquinoline **complex** was less sensitive to nuclease [9026-81-7] activity than free **DNA**. The interaction of chloroquine, primaquine, or I with RNA resulted in an increased sensitivity of the RNA to enzymic hydrolysis by several nucleases. Primaquine had little effect on the aminoacylation of transfer RNA in a mouse liver system assayed in the presence of 5 mM magnesium [7439-95-4] ions. Interaction of the antimalarial aminoquinolines with **nucleic** acids and the consequent interference in **nucleic** acid synthesis and function may be one mode of the antimalarial activity of these compds. and be responsible for some of the toxic reactions of these drugs in animals.

=> d bib abs l23 20

L23 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:82379 HCAPLUS
DN 76:82379
TI Methyl Green-**DNA complex**. Displacement of dye by **DNA**-binding substances
AU Krey, Anne K.; Hahn, Fred E.
CS Dep. Mol. Biol., Walter Reed Army Inst. Res., Washington, D. C., USA
SO Eur. Biophys. Congr., Proc., 1st (1971), Volume 1, 223-7. Editor(s): Broda, E. Publisher: Verlag Wiener Med. Akad., Vienna, Austria. CODEN: 24KMAA
DT Conference
LA English
AB The triphenylmethane dye, methyl green (MG), forms a stable **complex** with double-stranded **DNA**; free MG in aq. soln. at pH 7.5 undergoes a mol. rearrangement to a colorless form. MG stabilized **DNA** to thermal denaturation and was released from **DNA** proportionally to the extent of strand sepn. The dye may be bound by electrostatic attraction of its pos. centers to **DNA** phosphates of perhaps both strands. MG in its **complex** with **DNA** exhibited flow dichroism, indicating a high degree of order of dye mols. in the **complex**. Certain **DNA-complexing** substances, e.g. quinacrine and chloroquine, are known to displace MG from **DNA**. Rates of MG displacement produced by a series of **DNA-complexing** drugs and dyes were detd. The rate-detg. process was the liberation of MG rather than its subsequent rearrangement. Some displacements, particularly by compds. which displaced MG rapidly and almost completely, changed from an initial 1st-order to a subsequent 2nd-order kinetic course while for others a reaction order could not be established unambiguously. Substances which bind to **DNA** by intercalation displaced MG at more rapid rates and to larger extents than did nonintercalators. MG itself is not considered to bind to **DNA** by intercalation. We propose that the release of MG from **DNA** is caused by local unwinding of the double helix.

=> d bib abs 123 21

L23 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1969:10338 HCAPLUS
DN 70:10338
TI Binding of primaquine, pentaquine, pamaquine, and plasmocid to deoxyribonucleic acid
AU Whichard, Leona P.; Morris, Carl R.; Smith, Judy M.; Holbrook, David J., Jr.
CS Sch. of Med., Univ. of North Carolina, Chapel Hill, N. C., USA
SO Mol. Pharmacol. (1968), 4(6), 630-9
CODEN: MOPMA3
DT Journal
LA English
AB The binding of four 8-aminoquinoline antimalarials (primaquine, pentaquine, pamaquine, and plasmocid) to native and denatured calf thymus **DNA** was studied by equil. dialysis and direct spectrophotometry. The binding of the 8-aminoquinolines to **DNA** is (a) accompanied by a decrease in absorbance of the ligand, (b) decreased by an increase in ionic strength, (c) decreased by addn. of Mg2+ to a greater extent than would be expected from ionic strength effects alone, and (d) decreased under some conditions by the presence of 4M urea. In 0.01M K phosphate (pH 6), the total binding of the 8-aminoquinolines to various **DNA** prepns. at **DNA** nucleotide-to-aminoquinoline ratios .gtoreq.6 occurs in the following order: native **DNA** = denatured **DNA** > native **DNA** in 4M urea > denatured **DNA** in 4M urea. At low ionic strengths and pH 6, the binding of the singly protonated 8-aminoquinolines is less than, but comparable to, the binding of chloroquine, a divalent cation at the same pH. At a **DNA** nucleotide-to-aminoquinoline ratio of 10 and an ionic strength of 0.012 (pH 6), the percentages of the aminoquinolines bound to native **DNA** decrease in the following order: chloroquine > pentaquine > plasmocid > primaquine > pamaquine. At ionic strength .gtoreq.0.15, the binding of pentaquine and plasmocid equals or exceeds the binding of chloroquine to native **DNA**. Evidence is presented for the occurrence of at least 2 spectrally distinct bound forms for each 8-aminoquinoline.

=> d bib abs 123 22

L23 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2000 ACS
AN 1967:486135 HCAPLUS
DN 67:86135
TI Hueckel molecular orbital calculations for some antimalarial drugs and related molecules
AU Singer, Judith A.; Purcell, William P.
CS Dep. of Med. Chem., Univ. of Tennessee, Memphis, Tenn., USA
SO J. Med. Chem. (1967), 10(5), 754-62
CODEN: JMCMAR
DT Journal
LA English
AB Hueckel M.O. (H.M.O.) .pi. electronic charge ds. and energy levels of the highest occupied M.O. (H.O.M.O.) and lowest empty M.O. (L.E.M.O.) of several representative antimalarial compds. and their parent compds. have been calcd. Comparison of results on the antimalarial mols. quinine, chloroquine, primaquine, quinacrine, pyrimethamine, proguanil, cycloguanil, and 3-piperonylsydnone with those on their appropriate parent or analogous mols. have elucidated the contributions of the substituents to the .pi. electronic properties of the antimalarials. The interaction between components of the antimalarial **complex** between 2-hydroxy-4,6-dimethylpyrimidine and 4,4'-dinitrocarbanilide was studied. The specificity of this interaction seems to result from the fact that 4,4'-dinitrocarbanilide has a bonding L.E.M.O. The electronic aspects of the interaction with **DNA** of the antimalarials, quinine, chloroquine, and quinacrine, were investigated with inclusion of the effect of amine salt formation on electronic properties of antimalarials. The exptl. observed specific interaction of chloroquine with the guanine of **DNA** seems to be explained satisfactorily by electron-donating or accepting characteristics of these mols. 35 references.

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=> d pn ti 1-9

L38  ANSWER 1 OF 9  USPATFULL
PI     US 6090406  20000718
TI     Potentiation of immune responses with liposomal adjuvants

L38  ANSWER 2 OF 9  USPATFULL
PI     US 5916588  19990629
TI     Peptide-containing liposomes, immunogenic liposomes and methods of
       preparation and use

L38  ANSWER 3 OF 9  USPATFULL
PI     US 5614529  19970325
TI     Inhibition of plasmodia parasites by camptothecin compounds

L38  ANSWER 4 OF 9  USPATFULL
PI     US 5541164  19960730
TI     2-halo-2'-deoxyadenosines in the treatment of monocyte-mediated
       inflammatory disease conditions

L38  ANSWER 5 OF 9  USPATFULL
PI     US 5506213  19960409
TI     Adminstration of 2'-halo-2'-deoxy adenosine to treat inflammatory bowel
       disease

L38  ANSWER 6 OF 9  USPATFULL
PI     US 5318979  19940607
TI     Method of inhibiting the activity of cryptosporidium parvum

L38  ANSWER 7 OF 9  USPATFULL
PI     US 5278173  19940111
TI     Method of inhibiting the activity of human immunodeficiency virus (HIV)
       in vivo

L38  ANSWER 8 OF 9  USPATFULL
PI     US 5153202  19921006
TI     Method of inhibiting the activity of human immuno deficiency virus (HIV)
       in vivo

L38  ANSWER 9 OF 9  USPATFULL
PI     US 5106837  19920421
TI     Adenosine derivatives with therapeutic activity
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(not displayed dupl of 4)

(not displayed (duplicate of 8)

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=> d bib abs 138 1

L38  ANSWER 1 OF 9  USPATFULL
AN     2000:91561  USPATFULL
TI     Potentiation of immune responses with liposomal adjuvants
IN     Popescu, Mircea C., Plainsboro, NJ, United States
       Weiner, Alan L., Lawrenceville, NJ, United States
       Recine, Marie S., Hamilton Township, NJ, United States
       Janoff, Andrew S., Yardley, PA, United States
       Estis, Leonard, Upton, MA, United States
       Keyes, Lynn D., Upton, MA, United States
       Alving, Carl R., Bethesda, MD, United States
PA     The Liposome Company, Inc., Princeton, NJ, United States (U.S.
       corporation)
PI     US 6090406  20000718
AI     US 1990-485388  19900226 (7)
RLI    Continuation-in-part of Ser. No. US 1989-425727, filed on 23 Oct 1989,
       now patented, Pat. No. US 5231112 which is a continuation-in-part of
       Ser. No. US 1985-773429, filed on 10 Sep 1985, now patented, Pat. No. US
       4891208 which is a continuation-in-part of Ser. No. US 1985-721630,
       filed on 10 Apr 1985, now patented, Pat. No. US 4721612 which is a
       continuation-in-part of Ser. No. US 1984-599691, filed on 12 Apr 1984,
       now abandoned And a continuation-in-part of Ser. No. US 1989-397777,
       filed on 23 Aug 1989, now abandoned which is a continuation-in-part of
       Ser. No. US 1989-277854, filed on 30 Nov 1989, now abandoned And a
       continuation-in-part of Ser. No. US 1988-236701, filed on 25 Aug 1988,
       now abandoned And a continuation-in-part of Ser. No. US 1988-236702,
       filed on 25 Aug 1988, now abandoned And a continuation-in-part of Ser.
       No. US 1988-277854, filed on 30 Nov 1988, now abandoned And a
       continuation-in-part of Ser. No. US 1987-128974, filed on 4 Dec 1987,
       now abandoned And a continuation-in-part of Ser. No. US 1987-61186,
       filed on 11 Jun 1987, now abandoned which is a continuation-in-part of
       Ser. No. US 1986-934151, filed on 24 Nov 1986, now abandoned And a
       continuation-in-part of Ser. No. US 1986-873584, filed on 12 Jun 1986,
       now abandoned And a continuation-in-part of Ser. No. US 1988-236701,
       filed on 25 Aug 1988, now abandoned which is a continuation-in-part of
       Ser. No. US 1987-128974, filed on 4 Dec 1987, now abandoned And a
       continuation-in-part of Ser. No. US 1988-236702, filed on 25 Aug 1988,
       now abandoned
DT     Utility
EXNAM  Primary Examiner: Dees, Jose' G.; Assistant Examiner: Hartley, Michael
       G.
LREP   Rubin, Kenneth B.; Goodman, Rosanne
CLMN   Number of Claims: 16
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 2615
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     A high integrity liposome comprising at least one stabile lipid and at
       least one peptide-like therapeutic agent associated with said liposome,
       adapted for parenteral administration to an animal, including a human,
       and method according to manufacture and use. Immunizing dosage forms
       comprising a liposome and an immunogen, wherein said liposome and
       immunogen are present in an immunization dose. Additionally, a dosage
       form, including such form particularly adapted to producing an immune
       response, comprising a salt according to an organic acid derivative of a
       sterol and an immunogen wherein said organic acid derivative of a sterol
       and immunogen are present in an immunization dose, and method according
       to use is disclosed. Further, a dosage form, including such form
       particularly adapted to producing an immune response, comprising
       dimyristoylphosphatidylcholine (DMPC)/cholesterol liposomes, optionally
       in an aluminum hydroxide gel, and an immunogen wherein said
       DMPC/cholesterol and immunogen are present in an immunization dose, and
       method according to use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs 138 2

L38 ANSWER 2 OF 9 USPATFULL
AN 1999:72283 USPATFULL
TI Peptide-containing liposomes, immunogenic liposomes and methods of preparation and use
IN Popescu, Mircea C., Plainsboro, NJ, United States
Weiner, Alan L., Lawrenceville, NJ, United States
Recine, Marie S., Hamilton Township, NJ, United States
Janoff, Andrew S., Yardley, PA, United States
Estis, Leonard, Upton, MA, United States
Keyes, Lynn D., Upton, MA, United States
Alving, Carl R., Bethesda, MD, United States
PA The Liposome Company, Inc., Princeton, NJ, United States (U.S. corporation)
PI US 5916588 19990629
AI US 1995-452549 19950525 (8)
RLI Continuation-in-part of Ser. No. US 1993-108822, filed on 18 Aug 1993 76 Ser. No. US 1990-485388, filed on 26 Feb 1990 which is a continuation-in-part of Ser. No. US 108822 Ser. No. Ser. No. US 1989-397777, filed on 23 Aug 1989, now abandoned Ser. No. Ser. No. US 1988-277854, filed on 30 Nov 1988, now abandoned And Ser. No. US 1988-236701, filed on 25 Aug 1988 , said Ser. No. US 397777 which is a continuation-in-part of Ser. No. US 1988-277854, filed on 30 Nov 1988 Ser. No. Ser. No. US 1988-236702, filed on 25 Aug 1988, now abandoned And Ser. No. US 236701 , said Ser. No. US 277854 which is a continuation-in-part of Ser. No. US 1987-128974, filed on 4 Dec 1987, now abandoned which is a continuation-in-part of Ser. No. US 1987-61186, filed on 11 Jun 1987, now abandoned which is a continuation-in-part of Ser. No. US 1986-934151, filed on 24 Nov 1986 And Ser. No. US 1986-873584, filed on 12 Jun 1986, now abandoned , said Ser. No. US 277854 which is a continuation-in-part of Ser. No. US 61186 , said Ser. No. US 236701 which is a continuation-in-part of Ser. No. US 277854 And Ser. No. US 128974 , said Ser. No. US 108822 which is a continuation of Ser. No. US 1991-758587, filed on 12 Sep 1991, now patented, Pat. No. US 5288499 which is a division of Ser. No. US 1989-425727, filed on 23 Oct 1989, now patented, Pat. No. US 5231112 which is a continuation-in-part of Ser. No. US 1985-773429, filed on 10 Sep 1985, now patented, Pat. No. US 4891208 which is a continuation-in-part of Ser. No. US 1985-721630, filed on 10 Apr 1985, now patented, Pat. No. US 4721612 which is a continuation-in-part of Ser. No. US 1984-599691, filed on 12 Apr 1984, now abandoned
DT Utility
EXNAM Primary Examiner: Achutamurthy, Ponnathapura
LREP Rubin, Kenneth; Goodman, Rosanne
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2619
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A high integrity liposome comprising at least one stabile lipid and at least one peptide-like therapeutic agent associated with the liposome, adapted for parenteral administration to an animal, including a human, and method according to manufacture and use.

Immunizing dosage forms comprising a liposome and an immunogen, wherein the liposome and immunogen are present in an immunization dose. Additionally, a dosage form, including such form particularly adapted to producing an immune response, comprising a salt according to an organic acid derivative of a sterol and an immunogen are present in an immunization dose, and method according to uses is disclosed. Further, a dosage form, including such form particularly adapted to producing an immune response, comprising dimyristolyphosphatidylcholine (DMPC)/cholesterol liposomes, optionally in an aluminum hydroxide gel, and an immunogen wherein the DMPC/cholesterol and immunogen are present in an immunization dose, and method according to use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 2

L38 ANSWER 2 OF 9 USPATFULL

SUMM Liposomes are completely closed lipid bilayer **membranes** containing an entrapped aqueous volume. Liposomes may be unilamellar vesicles (possessing a single bilayer **membrane**) or multilamellar vesicles (onion-like structures characterized by multiple **membrane** bilayers, each separated from the next by an aqueous layer). The bilayer is composed of two lipid monolayers having a hydrophobic "tail" region and a hydrophilic "head" region. The structure of the **membrane** bilayer is such that the hydrophobic (nonpolar) "tails" of the lipid monolayers orient toward the center of the bilayer while. . .

SUMM . . . reference. Vesicles made by this technique, called LUVETS, are extruded under pressure once or a number of times through a **membrane** filter.

SUMM . . . of a sterol (such as citric acid), an amino acid derivative of a sterol or a salt form of a **polyamino** acid derivative of a sterol, or a salt form of a polycarboxylic acid derivative of a sterol. In one preferred. . .

SUMM . . . vaccine or immunogenic dosage form of this invention, the immunogen may be selected from the group comprising proteins, peptides, polysaccharides, **nucleic** acids, lipids, glycolipids, lipoproteins, lipopolysaccharides, synthetic peptides, bacterial fractions, viral fractions, protozoal fractions, tissue fractions, and cellular fractions. Specific immunogens. . .

SUMM . . . atoms), hydroxy acid derivatives of sterols (such as citric acid), amino acid derivatives of sterols or salt forms of a **polyamino** acid derivative of a sterol, or salt forms of a polycarboxylic acid derivative of a sterol.

SUMM . . . present invention liposomes of sufficient structural integrity for the intended use may be designed by varying the rigidity of lipid **membrane** constituents or by varying the proportion in which stabile lipid is admixed with a diluent or secondary lipid. In the. . .

SUMM . . . the sterols include but are not limited to, the carboxylic acids, dicarboxylic acids, polycarboxylic acids, hydroxy acids, amino acids and **polyamino** acids. Because the salt forms increase the water solubility of organic acids, any organic acid may be used to derivatize. . . susceptible to hydrolysis and, therefore, advantageous in the practice of the present invention); and any of the amino acids and **polyamino** acids.

DETD . . . lipid dislodged from the flask walls by swirling. In this example the material to be entrapped was human serum albumin **conjugated** to tritiated galactose ("galactose-albumin") and primaquine ("galactosealbumin-primaquine"). The galactose-albumin-primaquine in 0.3 ml of aqueous solution was added to the 5. . .

DETD **Conjugate** formation was effected by simultaneous sonication and drying of the mixture using a gentle stream of nitrogen. Sonication and drying were discontinued when no odor of ether could be detected. The **conjugate** material was in the form of a paste which was washed with 10-20 ml of phosphate buffered saline (PBS). This. . .

DETD . . . at 37.degree. C. for 2 hours and were washed twice with PBS. 200 ul of rabbit anti-guinea pig IgG-horseradish peroxidase **conjugate** (Cappel, Cooper Biomedical, Malvern, Pa.; 1:20,000 in 10% calf serum in 0.5.times.PBS) was added to all wells and the plates. . .

CLM What is claimed is:
. . . or ester linkage, wherein the organic acid is selected from the group consisting of carboxylic, dicarboxylic, polycarboxylic, hydroxy, amino and **polyamino** acids and wherein the liposome is present in the dosage form in an immunization dose.

IT **90-34-6**, Primaquine 816-94-4, Distearoyl phosphatidylcholine
9007-12-9, Calcitonin 18194-24-6, Dimyristoyl phosphatidylcholine
(peptide-contg. liposomes, immunogenic liposomes and methods of prepn. and use)

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=> d bib abs l38 3

L38  ANSWER 3 OF 9  USPATFULL
AN      97:25043  USPATFULL
TI      Inhibition of plasmodia parasites by camptothecin compounds
IN      Wall, Monroe E., Chapel Hill, NC, United States
        Wani, Mansukh C., Durham, NC, United States
        Engle, Robert R., 8305 Tuckerman La., Potomac, MD, United States  20854
        Miller, Robert E., 6742 Meadowside Dr., Frederick, MD, United States
        21702
PA      Research Triangle Institute, Research Triangle Park, NC, United States
        (U.S. corporation)
        Engle, Robert R., Potomac, MD, United States (U.S. individual)
        Miller, Robert E., Frederick, MD, United States (U.S. individual)
PI      US 5614529  19970325
AI      US 1994-309467  19940922 (8)
DT      Utility
EXNAM   Primary Examiner: Goldberg, Jerome D.
LREP    Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
CLMN    Number of Claims: 14
ECL     Exemplary Claim: 1
DRWN    No Drawings
LN.CNT 606
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Camptothecin compounds are effective inhibitors of plasmodia growth and
        are useful in treating plasmodia infections in livestock, other domestic
        animals and humans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 3

L38  ANSWER 3 OF 9  USPATFULL
SUMM    . . . I inhibiting activity" is meant a camptothecin compound which
        exhibits an IC.sub.50 value for topoisomerase I inhibition by the
        clearable complex assay of Hsiang et al. of 1.0 .mu.M or less.
        The ability of camptothecin compounds to inhibit the enzyme
        topoisomerase I can be readily evaluated using the cleavable
      complex assay described in U.S. Pat. No. 5,244,903 and Hsiang et
        al., (1985), J. Biol Chem., 260:14875-14878. Particularly preferred
        compounds are. . .
SUMM    . . . be administered in the form of liposome or microvesicle
        preparations. Liposomes are microvesicles which encapsulate a liquid
        within lipid or polymeric membranes. Liposomes and
        methods of preparing liposomes are known and are described, for example,
        in U.S. Pat. Nos. 4,452,747, 4,448,765, 4,837,028,. . .
DETD    . . . .sup.3 H-hypoxanthine was added to each well of the MTP to
        determine if the parasites could still replicate or repair DNA
        . After 66 hr of total incubation time, the MTP were frozen to lyse the
        erythrocytes and parasites. The parasite DNA was recovered by
        harvesting the lysate onto glass-fiber filters using a Mark II
        cell-harvester (Torntec, Orange, Conn.). The radioactivity was. . .
CLM     What is claimed is:
  . . . method of claim 1, wherein said camptothecin compound exhibits an
        IC.sub.50 value of 1.0 .mu.M or less in a cleavable complex
        assay for topoisomerase I inhibitory activity.

IT     54-05-7, Chloroquine   58-14-0, Pyrimethamine   83-89-6, Quinacrine
       86-42-0, Amodiaquin 90-34-6, Primaquine   130-95-0, Quinine
       500-92-5, Chloroguanide   525-61-1, Quinocide   564-25-0, Doxycycline
       738-70-5, Trimethoprim   2447-57-6, Sulfadoxine   7689-03-4D,
       Camptothecin, derivs.   53230-10-7, Mefloquine   63968-64-9, Artemisinin
       69756-53-2, Halofantrine   78287-27-1   78287-28-2   86639-63-6
       86639-64-7   91421-43-1   91421-49-7   124622-68-0   124622-76-0
       135014-21-0   135014-26-5   135415-73-5   169900-78-1   172546-50-8
       175614-94-5   175614-95-6   175614-96-7   175775-87-8
```

(inhibition of Plasmodium parasites by camptothecin compds.)

=> d bib abs 138 4

L38 ANSWER 4 OF 9 USPATFULL
AN 96:67984 USPATFULL
TI 2-halo-2'-deoxyadenosines in the treatment of monocyte-mediated inflammatory disease conditions
IN Carson, Dennis A., Del Mar, CA, United States
Carrera, Carlos J., San Diego, CA, United States
PA The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
PI US 5541164 19960730
AI US 1994-233056 19940426 (8)
RLI Division of Ser. No. US 1992-838546, filed on 19 Feb 1992, now patented, Pat. No. US 5310732 which is a continuation-in-part of Ser. No. US 1990-460351, filed on 3 Jan 1990, now patented, Pat. No. US 5106837 which is a continuation-in-part of Ser. No. US 1989-323350, filed on 14 Mar 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-169618, filed on 16 Mar 1988, now abandoned which is a continuation-in-part of Ser. No. US 1986-825215, filed on 3 Feb 1986, now abandoned
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Crane, L. Eric
LREP Welsh & Katz, Ltd.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1,6
DRWN 7 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1932
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel adenine derivatives whose structures are represented by Formula I, are disclosed, as are methods of using those compounds and others of Formula II to treat monocyte-mediated disorders such as rheumatoid arthritis and multiple sclerosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 4

L38 ANSWER 4 OF 9 USPATFULL
SUMM Synthesis of **DNA** complementary to viral RNA is thought to be required for both retroviral integration into host **DNA** and for the generation of new virions. For this reason, the HIV-encoded reverse transcriptase is a logical target for the. . .
SUMM . . . of HIV reverse transcriptase activity. Yarchoan et al. (1986) Lancet, 1:575-580, administered AZT to patients with AIDS or AIDS-related disease **complexes**. The drug was reportedly well tolerated and crossed the blood/brain barrier.
SUMM Those 2',3'-dideoxynucleoside 5'-triphosphates are also utilized by mammalian **DNA polymerases** beta and gamma. Waquar et al. (1984) J. Cell. Physiol., 121:402-408. They are, however, poor substrates for **DNA polymerase-**alpha, the main enzyme responsible for both repair and replicative **DNA** synthesis in human lymphocytes. In part, these properties may explain the selective anti-HIV activity of the 2',3'-dideoxynucleosides.
SUMM . . . made in clinical trials with AZT. Those results, in part, have shown that treatment of patients with AIDS or AIDS-related **complex** with AZT has resulted in elevation of CD4 (T4) peripheral blood cell counts, restoration of cutaneous delayed hypersensitivity, and reduction. . .
SUMM A second form of autoimmune disease involves the formation of immune **complexes** of autoantibody plus self-antigen that can fix complement as well as initiate inflammatory processes. Organs in which such **complexes** deposit are subject to inflammation, and ultimately to destruction. **Nucleic** acids are known to serve as antigens for this mechanism in systemic lupus erythematosus (SLE). Immune **complex** deposition appears to account for the

glomerulonephritis present in many autoimmune disorders.

SUMM The deposition of immune **complexes** on or in the synovia of joints appears to initiate or exacerbate an inflammatory response of the synovial **membrane** in rheumatoid arthritis. The deposited **complexes** fix and activate complement, which subsequently stimulates the attraction of inflammatory cells such as monocytes and macrophages. The deeper layers. . . . cells elaborate several effector molecules of the inflammatory response, which transforms the joint fluid into an inflammatory exudate. The immune **complexes** together with the infiltrating cell-released factors activate the clotting pathway leading to fibrin production and deposition in the joint space,. . .

DRWD FIG. 4 is a graph of the dose- and time-dependence for CdA in inducing **DNA** strand breaks in monocytes in vitro.

DRWD . . . hours. The effects of CdA exposure upon monocyte viability (open squares), AND content (closed squares), RNA synthesis (open circles) and **DNA** strand breaks (ds-**DNA**; closed circles) are illustrated.

DETD . . . to accumulate in the cells, much the same as an adenine derivative useful herein accumulates in the cells. Lymphocytopenia and **DNA** strand breaks observed by the treatment are believed to be mediated by accumulation of deoxyadenosine nucleotides.

DETD . . . or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, including **polymeric** acids or mixtures of such acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate phthalate, and the like. A particularly suitable enteric coating comprises a styrene-maleic acid **copolymer** together with known materials that contribute to the enteric properties of the coating. Methods for producing enteric coated tablets are. . .

DETD . . . kills viruses (or inhibits viral replication) by entering cells that are invaded by the viruses and presumably incorporating into growing **DNA** chains resulting in termination of the chains and subsequent inhibition of viral replication within these cells and further infection.

DETD . . . Z is present, is of particular interest since those materials, per se, are most likely not incorporated into a growing **polynucleotide** chain because the presence of the N-oxide group probably interferes with hydrogen bonding during that synthesis. Rather, it is believed. . .

DETD . . . being free from a net ionic charge, but possessing an internal zwitterionic charge pair, the N-oxide compounds can penetrate cell **membranes**. Those compounds are also somewhat more water-soluble than are the corresponding un-oxidized compounds.

DETD . . . intracellularly until such time as the N-oxide function is reduced and the nucleotide is incorporated to terminate the appropriate, growing **polynucleotide** chain.

DETD **DNA** Damage in Monocytes Exposed to CdA

DETD Monocytes were plated as discussed previously, and were then contacted with compositions containing various concentrations of CdA. The amount of **DNA** damage in monocytes exposed to CdA was determined by the fluorescent assay for **DNA** unwinding in alkaline solution described by Birnboim and Jevcak (1981) Cancer Res., 41:1889-1892, modified to accommodate lower cell numbers (Thierry. . .

DETD The unwinding rate of **DNA** in alkaline solution at 15 degrees C. is proportional to the number of **DNA** strand breaks or alkali-labile sites. The ethidium bromide fluorescence of residual duplex **DNA** in samples exposed to pH 12.8 for one hour was compared to the fluorescence of a **DNA** aliquot that was not exposed to alkali. The percent residual double-stranded **DNA** at 1 hour was taken as a measure of the **DNA** damage in the sample. The results are illustrated in FIG. 4.

DETD **DNA** breaks appeared within 2 hours in human monocytes exposed to 10 nM CdA, and accumulated with time during CdA exposure. The level of **DNA** damage was dose-dependent.

DETD The repair of monocyte **DNA** damage caused by CdA was compared to the damage caused by gamma irradiation. Monocytes were pre-exposed to 0.1 or 1.0 .mu.M CdA for four hours. At the end of this time, approximately 60 percent residual double-stranded **DNA** was present in the cells. The CdA was removed, and the amount of residual

double-stranded **DNA** was calculated over the next four hours. Any increase in double-stranded **DNA** represents ongoing repair mechanisms.

DETD Cells treated with 0.1 .mu.M CdA contained an additional 10 percent residual double-stranded **DNA** over the next four hours; cells treated with 1.0 .mu.M CdA showed no increase. In contrast, cells treated with gamma irradiation sufficient to cause a 60 percent reduction in double-stranded **DNA** (i.e., 40 percent residual double-stranded **DNA**) showed an additional 40 percent residual double-stranded **DNA**, to a total of 80 percent residual double-stranded **DNA**, over the next four hours. Therefore, the effects of CdA persist past the time of exposure, and the **DNA** damage caused by CdA exposure cannot be repaired as rapidly as an equivalent, or even greater, amount of damage caused. . .

DETD NAD.sup.+ consumption for poly(ADP-ribose) synthesis is a known consequence of severe **DNA** damage in eukaryotic cells. To determine the potential role of NAD depletion in the marked toxicity of CdA towards monocytes,. . .

DETD FIG. 5 shows the changes in oxidized AND in monocytes exposed to CdA. In contrast to measures of **DNA** integrity (double-stranded (ds)-**DNA**), the monocyte NAD content remained relatively constant during the first four hours of exposure, (>95 percent of control NAD), but. . .

DETD . . . reduction in RNA synthesis that was detectable after the first hour of culture, and was coincident with the appearance of **DNA** damage.

IT 53-03-2, Prednisone 54-05-7, Chloroquine 58-14-0, Pyrimethamine 63-74-1 **90-34-6**, Primaquine 100-33-4 107-36-8 599-79-1, Sulfasalazine 1397-89-3, Amphotericin B 7414-83-7 8064-90-2 16037-91-5 23256-30-6, Nifurtimox 53230-10-7, Mefloquine 128994-33-2
(monocyte-mediated disease treatment with substituted adenine derivs. and)

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=> d bib abs l38 6

L38  ANSWER 6 OF 9  USPATFULL
AN      94:49160  USPATFULL
TI      Method of inhibiting the activity of cryptosporidium parvum
IN      Davis, Michael H., 3020 E. Inglewood Ct., Springfield, MO, United States
        65804
PI      US 5318979  19940607
AI      US 1991-794614  19911115 (7)
RLI     Continuation of Ser. No. US 1989-418500, filed on 10 Oct 1989, now
        abandoned which is a continuation-in-part of Ser. No. US 1988-213822,
        filed on 30 Jun 1988, now abandoned
DT      Utility
EXNAM   Primary Examiner: Goldberg, Jerome D.
LREP    Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN    Number of Claims: 2
ECL     Exemplary Claim: 1
DRWN    No Drawings
LN.CNT 473
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A method for inhibiting the activity of cryptosporidium parvum in vivo
        comprises administering to a human host an antimalarial drug, which is
        capable of exhibiting a protective effect, a curative effect, or of
        preventing transmission of malaria in humans. The anti-malarial drug is
        primaquine and is administered to the human in an amount sufficient to
        prevent to at least inhibit infection by cryptosporidium parvum.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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=> d bib abs 138 7

L38 ANSWER 7 OF 9 USPATFULL
AN 94:3795 USPATFULL
TI Method of inhibiting the activity of human immunodeficiency virus (HIV) in vivo
IN Davis, Michael H., 3020 E. Inglewood Ct., Springfield, MO, United States 65804
PI US 5278173 19940111
AI US 1992-989496 19921210 (7)
RLI Continuation of Ser. No. US 1991-796244, filed on 25 Nov 1991, now abandoned which is a division of Ser. No. US 1991-690314, filed on 25 Apr 1991, now patented, Pat. No. US 5153202 which is a continuation of Ser. No. US 1990-560467, filed on 27 Jul 1990, now abandoned which is a continuation of Ser. No. US 1988-213811, filed on 30 Jun 1988, now abandoned
DT Utility
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 572
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting the activity of human immunodeficiency virus (HIV) in vivo comprises administering to a human host an antimalarial drug, which is capable of exhibiting a protective effect, a curative effect, or of preventing transmission of malaria in humans. The antimalarial drug is selected from the group consisting of

(a) alkaloids;

(b) 9-amino-acridines;

(c) 4-aminoquinolines;

(d) 8-aminoquinolines;

(e) biguanides;

(f) dihyrofolate reductase inhibitors;

(g) sulfones;

(h) sulfonamides;

(i) mefloquine;

(i) halofantrine;

(k) hydroxyanilino-benzo-naphtyridines; and

(l) sesquiterpene lactones.

The antimalarial drug is administered to the human in an amount sufficient to prevent or at least inhibit infection of T lymphocytes by HIV in vivo or to prevent or at least inhibit replication of HIV in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 7

L38 ANSWER 7 OF 9 USPATFULL
SUMM . . . human retroviruses with clear but limited relationship to isolates of HIV (for example, more than 20% but less than 50%

nucleic acid sequence identity) are not to be called HIV unless there are compelling biological and structural similiarities to existing members. . .

SUMM The existence of multiple human immunodeficiency viruses, such as HIV-1 and HIV-2, presents a **complex** epidemiologic picture. There is a common belief that an effective vaccine or pharmaceutical composition against HIV infection must be developed. . .

DETD (c) The virus encodes an RNA-dependent **DNA polymerase** (reverse transciptase) which is Mg2.sup.+ -dependent and can employ oligo(dT).sub.12-18 as a primer for reverse transcription from its 3' LTR;

DETD . . . established malaria infection. Further, antimalarial drugs include drugs that are useful for the prevention of infection of humans by malarial **vectors**, including drugs that intervene or interfere with the malaria parasite life cycle in a human host.

DETD . . . Biochimica et Biophysica Acta, 931:267-275 (1987). Proposed mechanisms included inhibition of lysosomal cathepsins, protonation within acidic intracellular compartments, stabilization of **membranes**, and enzyme induction. The net effect of antimalarial drugs in the prevention and treatment of malaria appears to be in. . .

DETD . . . approach for demonstrating the effectiveness of the antimalarial drugs involves detection of the virus by detecting unintegrated and integrated viral **DNA** as well as viral mRNA. Nature, 312:166-169 (1984). Southern and Northern blot hybridization techniques are useful in determination of the relative amounts of viral **DNA** and RNA of the virus-harboring cells and tissues. Science, 227:177-182 (1985). A probe can be constructed for integrated provirus using molecularly cloned labeled proviral **DNA**, and then one can determine in a **DNA** transfer experiment whether there is a proviral genome integrated in cellular **DNA** by hybridization. If only a few cells contain the provirus, in situ hybridization can be attempted.

DETD . . . a multiplicity of viral particles per cell and cultured in the presence or absence of antimalarial drugs. High molecular weight **DNA** is extracted at various times and assayed for its content of viral **DNA** using a radiolabelled HIV probe. Nature, 312:166-169 (1984). In the absence of antimalarial drugs under the culture conditions, viral **DNA** is detected. In contrast, in **DNA** from cells that have been completely protected by antimalarial drugs, neither unintegrated nor integrated **DNA** is detected.

DETD . . . detection of virus-positive cells and the characterization and comparison of viral isolates can be conducted using HIV-specific immunologic reagents and **nucleic** acid probes. F. Barre-Sinoussi et al., Science, 220:868-871 (1983); R. C. Gallo et al., Science 220:865-867 (1983).

IT 54-05-7, Chloroquine 56-54-2, Quinidine 58-14-0, Pyrimethamine 68-35-9, Sulfadiazine 83-89-6, Mepacrine 86-42-0, Amodiaquine **90-34-6**, Primaquine 130-95-0, Quinine 152-47-6, Sulfamethoxypyrazine 491-92-9, Pamaquine 500-92-5, Proguanil 525-61-1, Quinocide 723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 1220-83-3, Sulfamonomethoxine 2447-57-6, Sulfadoxine 27133-91-1 53230-10-7, Mefloquine 63968-64-9 69756-53-2, Halofantrine 74847-35-1, Pyronaridine 127513-08-0
(human immunodeficiency virus inhibition by)

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=> d bib abs 138 9

L38  ANSWER 9 OF 9  USPATFULL
AN     92:31859  USPATFULL
TI     Adenosine derivatives with therapeutic activity
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PI     US 5106837  19920421
AI     US 1990-460351  19900103 (7)
RLI    Continuation-in-part of Ser. No. US 1989-323350, filed on 14 Mar 1989,
       now abandoned And a continuation-in-part of Ser. No. US 1988-169618,
       filed on 16 Mar 1988, now abandoned which is a continuation-in-part of
       Ser. No. US 1986-825215, filed on 3 Feb 1986, now abandoned
DT     Utility
EXNAM  Primary Examiner: Brown, Johnnie R.; Assistant Examiner: Crane, L. Eric
LREP   Dressler, Goldsmith, Shore, Sutker & Milnamow, Ltd.
CLMN   Number of Claims: 4
ECL    Exemplary Claim: 1
DRWN   7 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1401
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Novel adenine derivatives whose structures are represented by Formula I,
       are disclosed, as are methods of using those compounds and others of
       Formula II to treat monocyte-mediated disorders and autoimmune diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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L38  ANSWER 9 OF 9  USPATFULL
SUMM   Synthesis of DNA complementary to viral RNA is thought to be
       required for both retroviral integration into host DNA and for
       the generation of new virions. For this reason, the HIV-encoded reverse
       transcriptase is a logical target for the. . .
SUMM   . . . of HIV reverse transcriptase activity. Yarchoan et al. (1986)
       Lancet, i:575-580, administered AZT to patients with AIDS or
       AIDS-related disease complexes. The drug was reportedly well
       tolerated and crossed the blood/brain barrier.
SUMM   Those 2',3'-dideoxynucleoside 5'-triphosphates are also utilized by
       mammalian DNA polymerases beta and gamma. Waquar et
       al. (1984) J. Cell. physiol., 121:402-408. They are, however, poor
       substrates for DNA polymerase-alpha, the main enzyme
       responsible for both repair and replicative DNA synthesis in
       human lymphocytes. In part, these properties may explain the selective
       anti-HIV activity of the 2',3'-dideoxynucelosides.
SUMM   . . . made in clinical trials with AZT. Those results, in part, have
       shown that treatment of patients with AIDS or AIDS-related
     complex with AZT has resulted in elevation of CD4 (T4)
       peripheral blood cell counts, restoration of cutaneous delayed
       hypersensitivity, and reduction. . .
SUMM   A second form of autoimmune disease involves the formation of immune
     complexes of autoantibody plus self-antigen that can fix
       complement as well as initiate inflammatory processes. Organs in which
       such complexes deposit are subject to inflammation, and
       ultimately to destruction. Nucleic acids are known to serve as
       antigens for this mechanism in systemic lupus erythematosus (SLE).
       Immune complex deposition appears to account for the
       glomerulonephritis present in many autoimmune disorders.
SUMM   The deposition of immune complexes on or in the synovia of
       joints appears to initiate the inflammatory response of the synovial
    membrane in rheumatoid arthritis. The deposited
     complexes fix and activate complement, which subsequently
       stimulates the attraction of inflammatory cells. The deeper layers of
       the synovium are infiltrated. . . cells elaborate several effector
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molecules of the inflammatory response, which transforms the joint fluid into an inflammatory exudate. The immune **complexes** together with the lymphocyte-released factors activate the clotting pathway leading to fibrin production and deposition in the joint space, synovium. . . .

DRWD FIG. 4 is a graph of the dose- and time-dependence for CdA in inducing **DNA** strand breaks in monocytes in vitro.

DRWD . . . period of 16 hours. The effects of CdA exposure upon monocyte viability (.quadrature.), NAD content (.quadrature.), RNA synthesis (.largecircle.) and **DNA** strand breaks (ds-**DNA** ;.largecircle.) are illustrated.

DETD . . . to accumulate in the cells, much the same as an adenine derivative useful herein accumulates in the cells. Lymphocytopenia and **DNA** strand breaks observed by the treatment are believed to be mediated by accumulation of deoxyadenosine nucleotides.

DETD . . . or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, including **polymeric** acids or mixtures of such acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate phthalate, and the like. A particularly suitable enteric coating comprises a styrene-maleic acid **copolymer** together with known materials that contribute to the enteric properties of the coating. Methods for producing enteric coated tablets are. . . .

DETD . . . kills viruses (or inhibits viral replication) by entering cells that are invaded by the viruses and presumably incorporating into growing **DNA** chains resulting in termination of the chains and subsequent inhibition of viral replication within these cells and further infection.

DETD . . . Z is present, is of particular interest since those materials, per se, are most likely not incorporated into a growing **polynucleotide** chain because the presence of the N-oxide group probably interferes with hydrogen bonding during that synthesis. Rather, it is believed. . . .

DETD . . . being free from a net ionic charge, but possessing an internal zwitterionic charge pair, the N-oxide compounds can penetrate cell **membranes**. Those compounds are also somewhat more water-soluble than are the corresponding un-oxidized compounds.

DETD . . . intracellularly until such time as the N-oxide function is reduced and the nucleotide is incorporated to terminate the appropriate, growing **polynucleotide** chain.

DETD EXAMPLE 4: **DNA** Damage in Monocytes Exposed to CdA

DETD Monocytes were plated as discussed previously, and were then contacted with compositions containing various concentrations of CdA. The amount of **DNA** damage in monocytes exposed to CdA was determined by the fluorescent assay for **DNA** unwinding in alkaline solution described by Birnboim and Jevcak (1981) Cancer Res., 41:1889-892, modified to accommodate lower cell numbers (Thierry. . . .

DETD The unwinding rate of **DNA** in alkaline solution at 15 degrees C is proportional to the number of **DNA** strand breaks or alkali-labile sites. The ethidium bromide fluorescence of residual duplex **DNA** in samples exposed to pH 12.8 for one hour was compared to the fluorescence of a **DNA** aliquot that was not exposed to alkali. The percent residual double-stranded **DNA** at 1 hour was taken as a measure of the **DNA** damage in the sample. The results are illustrated in FIG. 4.

DETD **DNA** breaks appeared within 2 hours in human monocytes exposed to 10 nM CdA, and accumulated with time during CdA exposure. The level of **DNA** damage was dose-dependent.

DETD NAD.sup.+ consumption for poly(ADP-ribose) synthesis is a known consequence of severe **DNA** damage in eukaryotic cells. To determine the potential role of NAD depletion in the marked toxicity of CdA towards monocytes,. . . .

DETD FIG. 5 shows the changes in oxidized NAD in monocytes exposed to CdA. In contrast to measures of **DNA** integrity [double-stranded (ds)-**DNA**], the monocyte NAD content remained relatively constant during the first four hours of exposure, (>95% of control NAD), but declined. . . .

DETD . . . reduction in RNA synthesis that was detectable after the first hour of culture, and was coincident with the appearance of **DNA** damage.

IT 53-03-2, Prednisone 54-05-7, Chloroquine 58-14-0, Pyrimethamine 63-74-1 **90-34-6**, Primaquine 100-33-4 107-36-8 599-79-1, Sulfasalazine 1397-89-3, Amphotericin B 7414-83-7 8064-90-2 16037-91-5 23256-30-6, Nifurtimox 53230-10-7, Mefloquine 128994-33-2
(monocyte-mediated disease treatment with substituted adenine derivs. and)